# Cervical dystonia

van den Dool, Joost

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# CERVICAL DYSTONIA

## Disability and the value of physical therapy

JOOST VAN DEN DOOL

**COLOPHON**

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# Cervical dystonia

## Disability and the value of physical therapy

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**Promotor**
Prof. dr. M.A.J. de Koning-Tijssen

**Copromotores**
Dr. B. Visser
Dr. J.H.T.M. Koelman

**Beoordelingscommissie**
Prof. dr. L.H.V. van der Woude
Prof. dr. C.P. van der Schans
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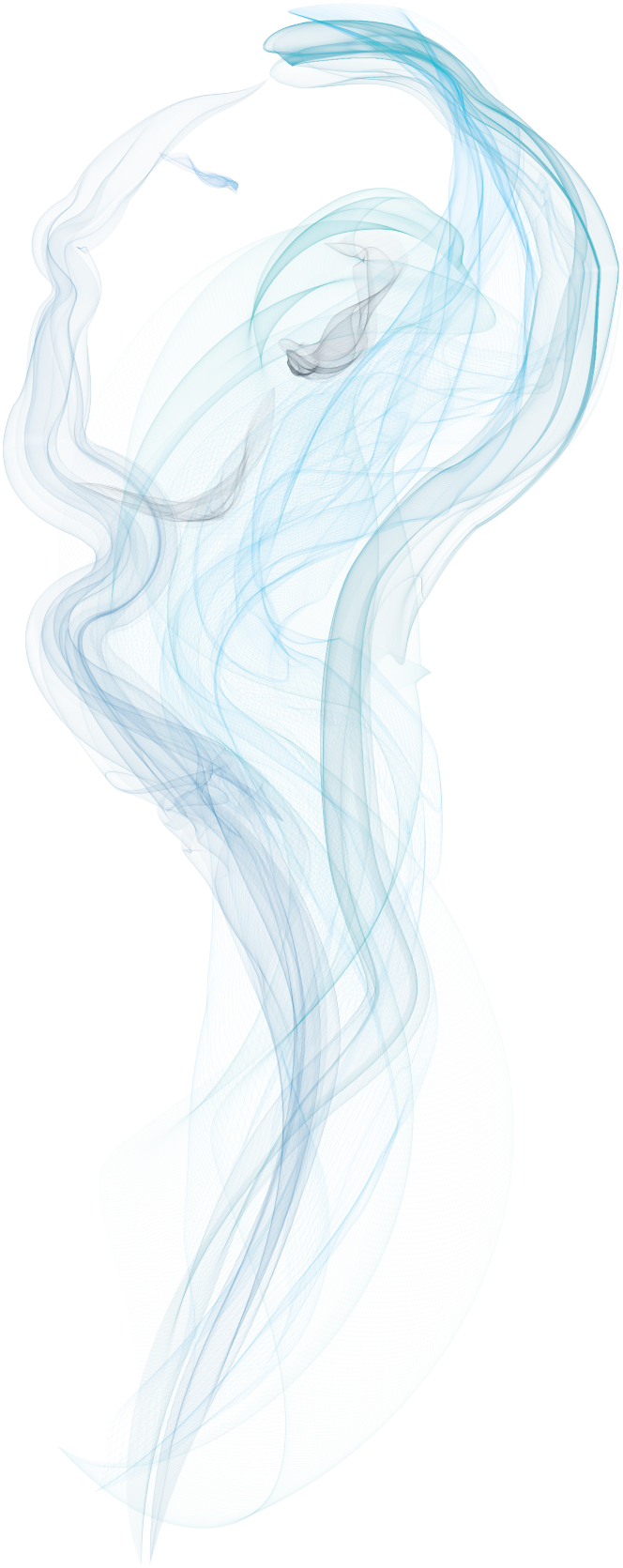


# CHAPTER 1

## Introduction and aim

*Based on the article Unmet needs in the management of Cervical Dystonia in Front. Neurol.2016; 7:165*

# DYSTONIA

Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. It is often initiated or worsened by voluntary action and associated with overflow muscle activation. [1] With an estimated prevalence in the range of 32 to 7.370 per million it is the third most common movement disorder after Parkinson's disease and essential tremor. [2]

Dystonia can be classified based on its clinical characteristics and etiology. [1] Clinical characteristics include body distribution, age at onset, temporal pattern and additional movement disorders or neurological features. Dystonia can be focal when involving one body part, segmental when two or more contiguous body regions are affected, multifocal when involving two non-contiguous or more body regions, generalized when the trunk and at least two other body sites are affected or hemidystonia if regions restricted to one body side are involved.[1] If dystonia presents during childhood (young-onset), it is likely that it started in one limb and gradually progresses to a generalized form, mostly due to a genetic cause. When starting during adult-hood (late-onset), dystonia is most likely to be idiopathic and isolated in one (focal) or two adjacent (segmental) body parts.[1]

## Cervical dystonia

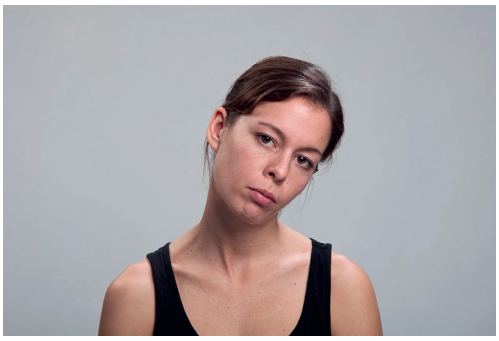
Cervical dystonia (CD), with a prevalence of 4.9 (95% CI 3.6 to 6.9) per 100,000 persons, is the most common form of focal dystonia.[3] It is characterized by involuntary muscle contractions causing abnormal postures and/or twisting movements of the head and neck.[4] Symptoms usually start after the age of 30 and mostly in the fifth decade of life.[3,4] Most patients show a combination of neck rotation (torticollis), flexion (anterocollis), extension (retrocollis), a sideways head tilt (laterocollis) or a lateral or sagittal shift (figure 1). Neck posturing may be either tonic, clonic or tremulous, and may result in permanent and fixed contractures.[5] A common clinical feature of cervical dystonia is the 'geste antagonistique' or 'sensory trick' when involuntary movements can be alleviated for a short period of time with a slight touch of the cheek, back of the head or neck.

# PATHOPHYSIOLOGY

The pathophysiology of cervical dystonia and dystonia in general is still largely unknown. Several genes have been associated with cervical dystonia, including ANO3, CIZ1, TOR1A, GNAL and THAP1. [6,7] However, these genes have been found in only a small percentage of CD patients.[8] Over the last decades scientific research on focal isolated dystonia's, including cervical dystonia, has identified several mechanisms that may contribute to development of dystonia. These mechanisms include

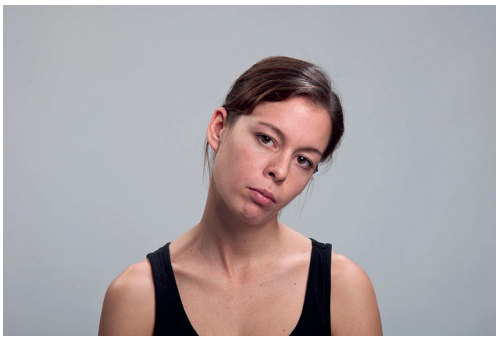
**Figure 1.** Example of different deviated postures in cervical dystonia.

Rotation



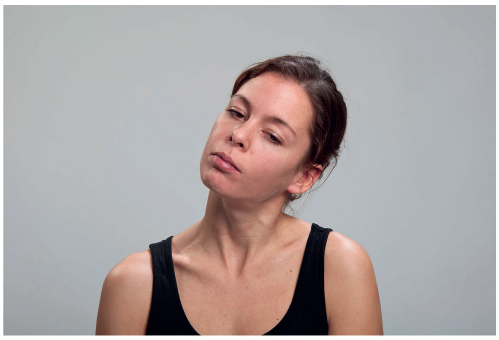
Lateroflexion

Anteflexion



Retroflexion

Shoulder elevation



Combination of deviated postures

abnormalities in the function of brain area's like the basal ganglia, the cerebellum, abnormal sensorimotor integration and maladaptive neuroplasticity of the motor areas and reduced inhibition of multiple levels of the nervous system involving movement [9,10,11] The mentioned mechanisms have also been found in motor areas representing body regions that do not display dystonic movements and in relatives of dystonia patients who are unaffected. [12–14] The findings of abnormalities in multiple regions of the brain, have led to the hypothesis that dystonia should be

seen as a network disorder where the primary defect most likely lies somewhere in the sensory-motor circuit connecting these regions.[15] It is thought that a genetic predisposition with external influences such as repetitive movements, trauma or stress may induce pathophysiological alterations at multiple levels in the central nervous system. However, the way these mechanisms interact causing dystonia remains uncertain.

## Non-motor symptoms

In recent years there is increasing awareness of non-motor symptoms in addition to the motor symptoms in dystonia patients. Pain is reported by two-third to three quarters of the patients.[16–19] Other non-motor symptoms are anxiety, depression, insomnia and fatigue.[20] Pain may be a consequence of motor symptoms but may also be related to depression and anxiety . [21,22] The prevalence of psychiatric disorders in CD can reach up to 91.4%, compared to 35% in the general population. [23] This could logically be the consequence of living with a chronic, visible and invalidating disorder. The extent of this difference is less when psychiatric disorders of CD patients are compared to those with other chronic and visible conditions like alopecia areata. However, CD patients still have a significantly higher risk to develop psychiatric co-morbidity. [24,25]

These non-motor manifestations are associated with impaired quality of life and the ability to perform daily life activities.[18,26]

## Disability

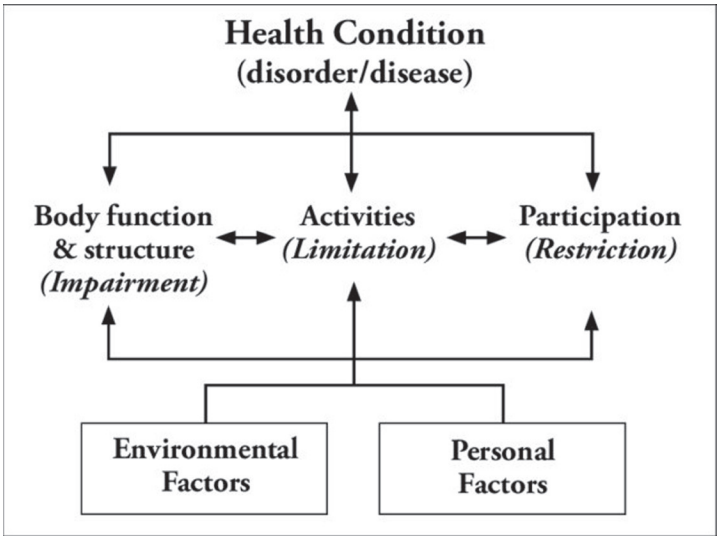
Both motor and non-motor symptoms may lead to a decreased ability to perform daily life tasks in CD patients.[26] Disability according the World Health Organization is an umbrella term covering problems and/or limitations in functions, activities and participation, combined with personal factors and environmental factors as defined in the international classification of functioning, disability and health (ICF) (table 1). [27]

**Table 1.** Definitions of the ICF

| | |
|---|---|
| **Body Functions** | Physiological functions of body systems (including psychological functions). |
| **Body Structures** | Anatomical parts of the body such as organs, limbs and their components. |
| **Impairments** | Problems in body function or structure such as a significant deviation or loss. |
| **Activity** | The execution of a task or action by an individual. |
| **Participation** | Involvement in a life situation. |
| **Activity Limitations** | Difficulties an individual may have in executing activities. |
| **Participation Restrictions** | Problems an individual may experience in involvement in life situations. |
| **Environmental Factors** | The physical, social and attitudinal environment in which people live and conduct their lives. |
| **Personal factors** | The particular background of a person's life and living situation with such as age, gender, race or social background. It also includes factors like lifestyle, coping strategies and individual psychological assets. |

The aim of the ICF classification is to provide a common language and framework for describing health and health-related states in order to improve communication between different users, such as health care workers, researchers and policy-makers. Functions are the result of physiological processes and anatomical structures of the body systems. In CD this applies to neurophysiological processes and affected muscles that continuous contract causing involuntary movements and abnormal postures. Activities are the execution of a task or action. For example a CD patient is not able to shave because of the continuous muscle contractions. Participation is involvement in a (social) life situation. Due to abnormal postures of the head, a CD patient might not be able to go to the theatre with friends because of the inability to maintain a neutral head posture to watch the play. Personal factors refer to gender, age, coping styles, social background and other factors that in influence how disability is experienced by the individual whereas environmental factors refer to certain context or environment a person lives in. For example placing the TV in the direction of the dystonic posture so a CD patient can comfortably watch a movie. Thus, disability is a complex phenomenon, reflecting an interaction between these different domains (figure 2).[27]

**Figure 2.** Schematic overview of the International Classification of Functioning, Disability & Health.[26] Reprinted with permission of the World Health Organisation.



# TREATMENT OF CERVICAL DYSTONIA

## Botulinum neurotoxin

Currently, treatment of cervical dystonia is mainly symptomatic and aimed at reducing, involuntary movements, to correct abnormal head postures and to treat pain. The best treatment option is to inject botulinum neurotoxin (BoNT) into the affected muscles.[28,29] BoNT binds on the peripheral cholinergic nerve endings at the neuromuscular junction and decreases the release of acetylcholine in the synaptic cleft. Therefore it blocks the neuromuscular transmission and reduces the contractions of the injected muscles.[30]

The effects of BoNT reach a peak effect within two to four weeks after injections, followed by a decrease of effects and return of symptoms. On average BoNT effects last for about three months before waring off and new injections are needed.[28] BoNT is proven to be effective in reducing the involuntary movements and abnormal postures in 70-92% of the patients.[31,32] Although BoNT is proven to be effective and the reduction of motor symptoms may also lead to a decrease of disability treatment is often unsatisfactory. Many patient maintain difficulties performing daily life tasks (figure 2).

## Oral pharmacotherapy

In case of an unsatisfactory response to BoNT treatment, CD patients can additionally be treated with oral pharmacotherapies to reduce symptoms such as trihexyphenidyl, baclofen or clonazepam.[33] Sound evidence for the effect of most oral pharmacotherapies on CD is lacking. The treatment regime is still based on the practitioner's personal preference.[33]

## Deep brain stimulation

For CD patients, who do not or no longer respond to BoNT or oral medical treatment, surgical treatment with deep brain stimulation (DBS) can be considered. In DBS electrodes are inserted into the brain delivering electrical pulses to the targeted structure probably blocking the signals that cause the symptoms of dystonia. The exact mechanisms behind the effects are still unclear. Krauss was the first to describe the beneficial outcome of DBS in the Globus Pallidus internus (GPi) on motor severity, pain and disability in three patients with CD. [34] Two other prospective studies and one randomized sham-controlled study also found beneficial effect of GPi stimulation on motor severity, pain, disability as well as mood.[35–37] The effects on quality of life were also investigated but only improved in a prospective study by Skogseid et al.[36] No between group differences were found on quality of life in a randomized sham-controlled study by Volkmann et al.[37]

## Physical therapy

In addition to BoNT treatment, most CD patients in the Netherlands are referred to physical therapy (PT) as many patients experience difficulties performing daily tasks despite the effects of BoNT treatment. The aim of PT is to decrease pain, muscle contractions and to improve the ability

to perform daily life activities. However, there is little evidence on the effectiveness of PT in CD and it is uncertain what should be the intensity and frequency of PT treatment and which intervention works best.[38,39]

In the available PT studies [40–42] BoNT treatment alone is compared to BoNT treatment with additional PT. The PT programs consist of short, intensive programs with various physical therapeutically interventions, varying from 40 minutes per session every other day for six weeks, up to 90 minutes a day for two weeks.[40–42] Despite significant improvements on pain and disability, the high intensity and frequency make implementation in daily practice difficult.

An internationally accepted and less intensive PT intervention was described by Bleton.[43] It aims to strengthen the (non-dystonic) antagonist muscles by repetitive exercises and to learn/re-learn motor skills. In two studies the effects of the Bleton method was compared to regular physical therapy.[41,44] Both studies show improvements on disability and pain over time but no differences between treatment groups were detected. Besides, none of these studies have investigated the effects of cervical dystonia on the long term. The effects of physical therapy on cervical dystonia therefore remain unclear.

## Pathology based physical therapy

It is hypothesised that physical therapy, and in particular the method used by Bleton, interacts with pathophysiological processes in cervical dystonia. By training the antagonist muscles, these muscles become stronger and more resilient against the dystonic movements. Besides training the antagonist muscles, treatment is also aimed at retraining normal and voluntary head movements which possibly alters the maladaptive neuroplastic changes related to dystonic movements. In writer's cramp, Bleton showed with cortical magnetoencephalography that the representation of the fingers of the affected hand normalize after a physical therapy program.[14] The representations were similar to those in healthy controls and were related to clinical improvement of writing. Unfortunately these findings are hard to replicate for cervical dystonia because the cortical representation of the neck muscles are rather small and hard to detect on magnetoencephalographic scans. A possible tool to map the cortical representation of the sternocleidomastoid muscle, a muscle frequently involved in many types of CD, is transcranial magnetic stimulation (TMS). [45] However, research is limited and more studies to find the exact location of neck muscle representation in the motor cortex are required.

A study by Thickbroom and colleagues in 2003 used TMS to the cortical representation of the abductor pollicis brevis muscle in patients with CD and showed displacement of upper limb corticomotor maps.[46] So there is some evidence on maladaptive neuroplastic changes in the motor cortex of CD patients. With these mechanisms in mind, PT treatment should be aimed at reversing the maladaptive changes to affect the pathophysiological mechanisms that are thought to play an important role in the development of CD. PT treatment should therefore be combined

with motor learning principles that have been found relevant for neuro rehabilitation and enhance neural plasticity.[47] Coaching and principles of providing feedback will help patients to apply the (re-)learned motor skills in daily life situations with the aim to decrease disability.[48,49]

## AIM AND OUTLINE OF THIS THESIS

This thesis aims to contribute to some unmet needs in the treatment of CD patients by assessing clinical issues in BoNT treatment that need further improvement, determinants of disability and the value of physical therapy in addition to BoNT treatment.

In **Chapter 2** a systematic review is performed to investigate clinical issues arising from the clinical practice concerning BoNT treatment and to provide evidence based recommendations for further improvement of BoNT treatment for CD.

In an attempt to determine the factors that cause disability in cervical dystonia patients, a factor analyses is performed on the baseline data that was collected for the study towards a specialized physical therapy program. The results of this analysis are presented in **Chapter 3a**.

Since many CD patients mention driving as an important daily life activity in which they encounter limitations, the effects of cervical dystonia is investigated on real-time driving performance in a small pilot simulator study. Outcomes of this study are described in **Chapter 3b.**

In **Chapter 4** we have developed a specialized PT program and a protocol for a large randomized controlled trial to investigate its effects on disability compared to regular physical therapy in cervical dystonia.

The results of the trial towards the effectiveness of the specialized PT program compared with regular PT are described in **Chapter 5**.

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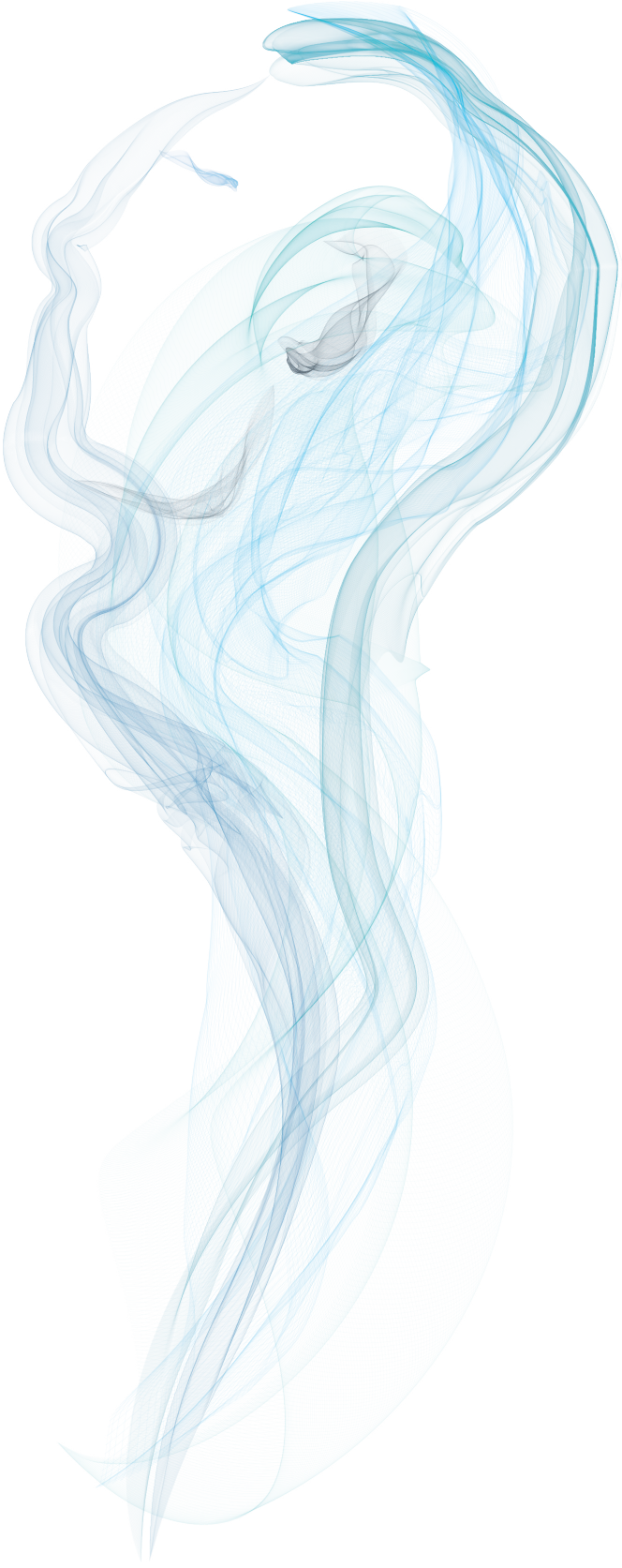

# CHAPTER 2

## Clinical practice: Evidence based recommendation for the treatment of Cervical Dystonia with Botulinum Toxin

Maria Fiorella Contarino, **Joost van den Dool**, Yacov Balash, Kailash Bhatia, Nir Giladi, Johannes H. Koelman, Annemette Lokkegaard, Maria J. Marti, Miranda Postma, Maja Relja, Matej Skorvanek, Johannes D. Speelman, Evelien Zoons, Joaquim J. Ferreira, Marie Vidailhet, Alberto Albanese and Marina A. J. Tijssen

*Frontiers in Neurology. 2017;8:35*

## ABSTRACT

Cervical dystonia (CD) is the most frequent form of focal dystonia. Symptoms often result in pain and functional disability. Local injections of botulinum neurotoxin are currently the treatment of choice for CD. Although this treatment has proven to be effective and is widely applied worldwide, many issues still remain open in the clinical practice. We performed a systematic review of the literature on botulinum toxin treatment for CD based on a question-oriented approach, with the aim to provide practical recommendations for the treating clinicians. Key questions from the clinical practice were explored. Results suggest that while the beneficial effect of botulinum toxin treatment on different aspects of CD is well established, robust evidence is still missing concerning some practical aspects, such as dose equivalence between different formulations, optimal treatment intervals, treatment approaches, and the use of supportive techniques including electromyography or ultrasounds. Established strategies to prevent or manage common side effects (including excessive muscle weakness, pain at injection site, dysphagia) and potential contraindications to this treatment (pregnancy and lactation, use of anticoagulants, neurological comorbidities) should also be further explored.

# INTRODUCTION

Cervical dystonia (CD) is the most frequent form of focal dystonia, with an overall prevalence of 4.98/100,000 in Europe. [1] CD is characterized by abnormal postures of head and neck that can considerably impair activities of daily living (ADL), with pain occurring in 43.1% of patients [2]. Mood disorders, including anxiety and depression, are frequently present. [3, 4]

Oral medication has a limited role. Trihexyphenidyl is classically proposed, but the tolerance profile is low. [5] Benzodiazepines, especially diazepam and clonazepam, mainly reduce dystonia-related pain, anxiety, and possibly dystonic tremor. [6] Tetrabenazine, although possibly effective, [7] is limited by the frequent side effect of depression and parkinsonism. Evidence on the effectiveness of allied care treatments, including physiotherapy and cognitive behavioral therapy, is scanty. [8] In those with unsatisfactory botulinum neurotoxin (BoNT) effect, surgery may be considered. Peripheral surgery, such as selective peripheral denervation, can provide improvement in about two-thirds of cases, with frequent relapses and is now rarely performed. [9, 10] Deep brain stimulation (DBS) of the globus pallidus pars interna appears to be a better choice, despite potential severe complications. [11] Alternative DBS targets, such as the subthalamic nucleus, need further investigation. [12]

Local injections of BoNT are currently the treatment of choice for CD. By binding to peripheral cholinergic nerve endings in the neuromuscular junction, BoNT decreases the release of acetylcholine at the motor neuron in the synaptic cleft, thus blocking neuromuscular transmission and provoking muscle weakness. [13]

Botulinum neurotoxin type A is the most frequently used; type B is only proposed in selected cases.

Although BoNT treatment is widely applied worldwide, many questions remain open in clinical practice.

Some aspects of this treatment have been largely explored in the literature, and robust evidence is available. Other aspects still deserve attention and univocal answers and directives are lacking.

In this paper, literature on BoNT treatment for CD was systematically reviewed based on a question-oriented practical approach. The aim was to provide practical recommendations on common issues in clinical practice. To this end, we reviewed the evidence concerning the comparison of different formulations of BoNT in improving motor symptoms, pain, and quality of life (QoL), also in relation to the dosage conversion ratio, which is a long debated topic.

Another common issue in the daily practice, which demands stronger evidence is how to prevent and manage side effects and complications, including the formation of neutralizing antibodies (NAB) and treatment side effects such as dysphagia, neck muscle paresis, or pain at injection site.

Due to the nature of the treatment itself, which involves intramuscular injections and a neurochemical denervation, questions may arise concerning potential contraindications such as the use of anticoagulants or the presence of concomitant neuromuscular disorders, in addition to pregnancy and lactation.

We finally explored issues related to the optimization of the treatment, including the optimal initial dose of BoNT, and whether injection strategy can be improved by applying multiple injection points instead of single injection points or by using neurophysiological techniques or associated physiotherapy. These topics have been touched upon in some studies, but the use of different methodologies, protocols, and sometimes patients' populations makes it difficult to directly compare the results.

## METHODS

The aim of this manuscript was to provide a literature review focused on some specific questions arising from the clinical practice. A structured literature review was conducted, by using appropriate keywords covering the topic of BoNT treatment for CD. A language restriction to English, French, German, and Dutch was applied. All kind of studies were reviewed and studies carried out before 1980 were excluded.

### Information sources

Three databases were searched: Medline and Embase using the Ovid interface, and the Cochrane library.

### Selection of papers

In all three databases, we identified systematic reviews, randomized controlled trials (RCTs), health economic evaluation studies, and, in both Medline and Embase, also observational studies. The complete search strategy is reported in File S1 in Supplementary Material.

### Review method

All the papers were screened for topic appropriateness on abstract basis by two independent reviewers with successive agreement on discrepancies. Papers were then assigned to different co-authors according to predefined key clinical questions. To assess the quality of the published studies, the classification scheme for level of evidence and the level of recommendation of the American Academy of Neurology was used [14] (File S2 in Supplementary Material). The recommendation level is reported for each statement.

# RESULTS

## Effect of different BoNT formulations on CD (Table 1)

Three BoNT-A products are commercially available: onabotulinumtoxinA (Botox®, Allergan), abobotulinumtoxinA (Dysport®, Ipsen), and incobotulinumtoxinA (Xeomin®, Merz). These products differ concerning the added preservatives, the toxin solubility, and the relative potencies. Only one type of BoNT-B is available: rimabotulinumtoxinB (Neurobloc®/Myobloc®, Elan Pharma).

**Are the different formulations of BoNT-A and BoNT-B effective in improving CD?**

Several RCTs showed that onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB are effective in reducing dystonia when compared to placebo. [15–25] One RCT showed that incobotulinumtoxinA (at both doses of 120 IU and 240 IU) significantly improved Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total scores compared to placebo in 233 CD patients [26] and that improvement of mean TWSTRS-total ($p < 0.001$) and severity score ($p < 0.016$) persisted after repeated injection (up to 5). [27]

*Conclusion and recommendations*

There is class I evidence that the three BoNT-A and the BoNT-B formulations significantly improve dystonia in CD. The recommendation level is A for abobotulinumtoxinA, onabotulinumtoxinA, and rimabotulinumtoxinB, and level B for incobotulinumtoxinA. [26]

**Does BoNT-A treatment improve QoL?**

In a double-blind RCT, treatment with 500 IU of abobotulinumtoxinA produced significantly greater improvements than placebo in Physical Functioning, Role Physical, Bodily Pain, General Health, and Role Emotional domains of the SF-36 ($p \leq 0.03$). [28]

*Conclusion and recommendations*

There is class I evidence that BoNT-A improves QoL in CD (level B).

**Does BoNT-A reduce pain associated with CD?**

In five RCTs with a total of 162 CD patients, 71% of the patients treated with onabotulinumtoxinA and abobotulinumtoxinA reported pain reduction compared with 12% of the patients in the placebo group ($p < 0.00001$). [29] Pain was also improved with incobotulinumtoxinA in both single-set injections and long-term treatment. [26, 27]

*Conclusion and recommendations*

There is class I evidence that BoNT-A reduces pain symptoms in CD (level A).

**Table 1.** Effect of different formulations of BoNT on cervical dystonia

| Question | Answer | Level of recommendation |
|---|---|---|
| **Is abobotulinumtoxinA effective in improving CD?** | Yes | A |
| **Is incobotulinumtoxinA effective in improving CD?** | Yes | B |
| **Is onabotulinumtoxinA effective in improving CD?** | Yes | A |
| **Is rimabotulinumtoxinA effective in improving CD?** | Yes | A |
| **Does BoNT-A treatment improve quality of life?** | Yes | B |
| **Does BoNT A reduce pain associated to CD?** | Yes | A |
| **Do BoNT A and BoNT B have a comparable effect and duration of effect on dystonia?** | Yes | A |
| **Do BoNT A and BoNT B have the same rate of side effects?** | No (Side effects are more frequent with BoNT B) | B |
| **What is the conversion ratio of onabotulinumtoxinA to abobotulinumtoxinA?** | 1 IU to 3 IU<br>1 IU to 2.5 IU | A<br>B |
| **What is the conversion ratio of onabotulinumtoxinA to incobotulinumtoxinA?** | 1 IU to 1 IU | B |

BoNT, Botulinum neurotoxin; CD, cervical dystonia; IU, international units.

### Do BoNT-A and BoNT-B have comparable effects?

In two RCTs [30, 31], no difference was found in the size and duration of effect on the total TWSTRS score and sub-scores (dystonia severity, limitations, and pain score) between BoNT-A and BoNT-B. Dry mouth and swallowing difficulties were more common with BoNT-B. [30, 32]

*Conclusion and recommendations*

Botulinum neurotoxin-A and BoNT-B have a comparable effect and duration of effect (level A). Side effects are more frequent with BoNT-B (class I evidence, level B).

### What is the conversion ratio of different formulations of BoNT-A?

The conversion factor between the different formulations is still a matter of discussion. OnabotulinumtoxinA vs. AbobotulinumtoxinA LD50 tests have shown 1:1 potency ratio of IncobotulinumtoxinA vs. onabotulinumtoxinA [33], and 2.3:1 of abobotulinumtoxinA vs. onabotulinumtoxinA. These data however cannot be directly translated into the clinical practice. [34] In a retrospective study, changing from onabotulinumtoxinA to abobotulinumtoxinA with a

conversion rate of 1:2 resulted in a tendency toward higher efficacy but more adverse events. [35] At 6.5 years follow-up, the doses had been reduced, and the median dose conversion ratio had decreased to 1:1.7. In a double-blind study, 79 healthy controls were randomized into 18 groups, receiving different doses and concentrations of onabotulinumtoxinA or abobotulinumtoxinA. [36] Both toxins caused a comparable, significant decline in the compound muscle action potential (CMAP). A statistical model with CMAP data indicated a bioequivalence of 1 IU onabotulinumtoxinA: 1.57 IU abobotulinumtoxinA and a maximum doseequivalence ratio of 1:3. In a comparative clinical study, 73 CD patients were randomized for onabotulinumtoxinA or abobotulinumtoxinA with a dose ratio of 1:3 IU. [37] The improvement of Tsui score, the duration of effect, and the rate of side effects were comparable. Two different conversion factors (1:3 and 1:4) between onabotulinumtoxinA and abobotulinumtoxinA were tested in a double-blind randomized three-period crossover study in 54 CD patients. [38] AbobotulinumtoxinA was significantly more effective than onabotulinumtoxinA in reducing Tsui score, with no significant difference between the two conversion ratios. The adverse events were more frequent in the abobotulinumtoxinA group, but only significantly for the 1:4 conversion. A recent double-blind, randomized, crossover study using a conversion ratio of 1:2.5 IU showed comparable efficacy and adverse effects. [39]

*Conclusion and recommendations*

It is recommended to use a conversion of 1 IU onabotulinumtoxinA to 3 IU abobotulinumtoxinA (level A) [37, 38], although conversion ratios of 1:2.5 might be equally safe and effective (class I, level B). [39]

**OnabotulinumtoxinA vs. IncobotulinumtoxinA**

In an open label prospective crossover study, 40 patients initially treated with onabotulinumtoxinA were randomly assigned to treatment switch to incobotulinumtoxinA with a 1:1 ratio. [33] Inter-injection intervals and treatment duration showed comparable efficacy for at least four injection cycles. Comparable efficacy on TWSTRS and adverse-event profiles for up to 16 weeks were also reported in a randomized, double-blind, parallel-group, non-inferiority trial, with CD patients randomized to incobotulinumtoxinA or onabotulinumtoxinA with the same conversion factor of 1:1. [40]

*Conclusion and recommendations*

It is recommended to use a conversion of 1:1 IU onabotulinumtoxinA to incobotulinumtoxinA (class I, level B).

## Optimization of BoNT treatment for CD (Table 2)

**What is the recommended initial BoNT dose for treatment of CD?**

According to the respective summary of product characteristics (SPC—last accessed 08/04/2015), the suggested starting total dose is 500 IU in two-three muscles, for abobotulinumtoxinA

(SPC last text revision 11/12/2013), and <200 IU (50 IU/injection and maximum 100 IU to the sternocleidomastoid) for onabotulinumtoxinA (SPC, 19/03/2015). For incobotulinumtoxinA, a total dose of 200 IU is mentioned, with doses up to 300 IU allowed (50 IU/injection—SPC, 16/11/2012). For rimabotulinumtoxinB, an initial dose of 5,000 IU may be considered, but a dose of 10,000 IU divided between two and four muscles may be more effective (SPC, 26/02/2014).

In an RCT, 73 patients were randomized into four groups treated with placebo, abobotulinumtoxinA 250, 500, or 1,000 IU, divided between one splenius capitis and the contralateral sternocleidomastoid muscle. [21] The greatest improvement was found in the group treated with 1,000 IU, although significantly more side effects were reported. An initial dose of 500 IU AbobotulinumtoxinA (divided into 100–200 IU in the sternocleidomastoid muscle, 250–350 IU in the splenius, 100–200 IU in the trapezius, and 100–200 IU in the levator scapulae) significantly improved CD with respect to placebo in another RCT on 68 patients. [41] Based on these results, an initial dose of 500 IU abobotulinumtoxinA is suggested. It is worth mentioning, however, that CD could be successfully treated using an average total dose of 200–400 IU abobotulinumtoxinA under electromyography (EMG) guidance, resulting also in fewer side effects. [42] A starting dose of 50–100 IU of onabotulinumtoxinA per muscle, with a maximum dose per session of 280 IU, was used in a study on 32 patients. A documented improvement in both subjective and objective parameters was observed in 75% of patients. [43] The mean total doses of original onabotulinumtoxinA injections, reported in 30 studies, as assessed by a systematic review, ranged from 60 to 374 IU in total. [44] In an RCT, both doses of 120 IU and 240 IU incobotulinumtoxinA significantly improved the TWSTRS-total scores compared to placebo in previously treated and treatment-naïve subjects, with mild side effects. Initial dose 120 IU of incobotulinumtoxinA has been suggested based on these results. [26] Three double-blind, randomized, placebo-controlled studies [20, 22, 23] have shown that the effect of botulinum toxin B injections in doses of 2,500, 5,000, and 10,000 IU was significantly higher compared to placebo, with the highest clinical effect seen with dose of 10,000 IU as measured by the TWSTRS-total score. The incidence of mild dysphagia was higher in the 10,000 IU group (16, 10, and 27%, respectively, as compared to no patient who received placebo). [20]

*Conclusion and recommendations*

An initial total dose of 500 IU abobotulinumtoxinA is effective (level A), although other dosages might be used. [41, 45] An initial total dose of 120 IU incobotulinumtoxinA is probably effective (evidence class I, level B). [26] No clear recommendations can be given on the optimal starting does of onabotulinumtoxinA (level U). An initial total dose of 2,500 or 5,000 IU rimabotulinumtoxinB (evidence class I, level B) or 10,000 IU (level A) is probably effective.

**Table 2** Optimization of BoNT treatment for cervical dystonia

| | | |
|---|---|---|
| **What is the recommended initial dose for treatment of CD with abobotulinumtoxinA?** | 500 IU (although other dosages might be used) | A |
| **What is the recommended initial dose for treatment of CD with incobotulinumtoxinA?** | 120 IU | B |
| **What is the recommended initial dose for treatment of CD with onabotulinumtoxinA?** | No recommendation | U |
| **What is the recommended initial dose for treatment of CD with rimabotulinumtoxinB?** | 2.500 or 5000 IU<br>10000 IU | B<br>A |
| **Can prior polymyographic-EMGand EMG guidance improve the treatment outcome in treatment-naïve patients?** | Yes | A |
| **Can prior polymyographic-EMG and EMG guidance improve the treatment outcome in in patients with deterioration of treatment effect?** | Yes | C |
| **Are multiple-points injections per muscle more effective than single-point injections?** | Yes | U |
| **Can additional physiotherapy improve the effect of BoNT treatment?** | No (motor improvement as measured by TWSTRS or Tsui score) | C |
| | Yes (disability and pain and prolongs the effect of BoNT) | U |

BoNT, Botulinum neurotoxin; CD, cervical dystonia; EMG, electromyography; IU, international units; TWSTRS, Toronto Western Torticollis Rating Scale

**Can prior polymyographic EMG (pEMG) and simultaneous EMG improve the treatment outcome?**

In one RCT, 52 CD patients were randomized into a pEMGgroup (treated muscles selected based on clinical evaluation and pEMG, and BoNT injected using simultaneous EMG) or control group (muscles selected based solely on clinical examination and injected without EMG). [46] Improvement on the TWSTRS was higher in the pEMG with EMG assistance group (14 vs. 5%). In a randomized prospective, blinded study on 26 treatment naive patients, the objectively measured clinical outcome was significantly better when the muscle selection was based on quantitative EMG and treatment was performed with simultaneous EMG, than when treatment was based on clinical judgment alone. [47] Other studies showed that without pEMG, 24–41% of the dystonic muscles were missed, and 25–35% of the injected muscles were misjudged as dystonic. [47–49]

A retrospective study explored results of treatment with pEMG in 40 patients with previously unsatisfactory treatment response. [50] After 1 year, a significant improvement in both Tsui scores and subjective evaluation was observed. pEMG led to change in injection pattern in 96% of the patients. In another study, 8/10 CD patients with deterioration of treatment effect, achieved marked improvement (64% on TWSTRS) after pEMG guided injections. [51] The identification of

motor endplate zones with high-density surface EMG may help decreasing the BoNT dose by keeping the effect unaltered. [52]

*Conclusion and recommendations*

There is class I evidence that, in treatment-naïve patients, improvements in dystonia and pain are greater if muscles are selected based on a combination of clinical examination and pEMG and injections are performed with EMG guidance (level A). [46,47] In patients with deterioration of treatment effect, the use of pEMG and EMG guidance can improve the results (class III, level C). [50,51]

**Are multiple-points injections per muscle more effective than single-point injections?**

No RCTs on this topic were found. A comparative study in 49 patients showed that multiple injections are more effective than a single injection in improving dystonia, pain, posture deformity, range of motion, and activity endurance. [53] Experts recommend the administration of one to four injections per muscle, depending on the volume of the muscle. [4,54]

*Conclusion and recommendations*

There are indications (class III) that multi-point BoNT injections are more effective than single-point BoNT injections (level U).

**Can physiotherapy improve the effect of BoNT treatment?**

In one single-blind RCT, no significant difference was found between patients randomized to BoNT treatment combined with relaxation therapy alone or with a 12-week physiotherapy program and relaxation therapy. [55] In one crossover RCT on 40 patients, significantly greater reductions in disability in ADL and subjective pain were observed after a 6-week additional physiotherapy, with respect to BoNT treatment alone. In addition, clinical benefit lasted longer and a lower BoNT dose was needed at reinjection. No significant differences were observed on the Tsui scale and TWSTRS. [56] In a case–control open study, 40 patients followed a 4-week physiotherapy program combined with BoNT treatment or BoNT treatment alone. The physiotherapy group showed significantly more improvement on the pain subscale of the TWSTRS, and on some subscales of the SF-36. [57]

*Conclusion and Recommendation*

Adding physiotherapy in combination with BoNT treatment does not produce a greater motor improvement as measured by TWSTRS or Tsui (class II, level C). [55] Adding physiotherapy to BoNT treatment may improve disability, pain, and prolong the effect of BoNT [class III [4] and IV [57], level U].

## Primary and secondary non-responsiveness (SNR) (Table 3)

Primary non-responsiveness to BoNT, defined as lack of treatment effect from the first application, and due to genetically induced resistance [58] or a prior (unnoticed) botulism [59], is exceptional. Technical aspects such as insufficient dosing, errors during drug storage and reconstitution, or

improper injection sites could also lead to an initial lack of response, usually amended in successive treatments.

Secondary non-responsiveness is defined as "insufficiently improved posture after three or more unsuccessful injection cycles in CD patient's previously achieving satisfactory results". [60] SNR concerns around 3–5% of the patients. [61]

The formation of NAB, with estimated frequency in CD patients varying from 1.2% [62] to 40% [63], is one of the causes of SNR. NAB have been found in patients treated with onabotulinumtoxinA, abobotulinumtoxinA, and rimabotulinumtoxinB. [64] RimabotulinumtoxinB seems more likely to elicit SNR than BoNT-A: antibody-induced therapy failure was shown in 44% of CD patients treated with BoNT-B during a short period. [65] The development and titer of NAB does not correlate with the entity of SNR, and there is evidence that the mere detection of NAB does not necessarily indicate the presence of SNR. [66, 67] No antibodies are described after treatment with incobotulinumtoxinA in naive CD patients, [68, 69] while this has been reported in one patient previously treated with another BoNT. [33]

Factors significantly associated with SNR include previous recourse to other therapies such as surgical interventions, physical therapy and neuroleptic use, a higher number of serious adverse events, more frequent treatment interruptions, and higher average BoNT-A doses during the last three injection cycles. [67]

**Table 3.** Primary and secondary non-responsiveness

| | | |
|---|---|---|
| **Are treatment intervals <12 weeks safe?** | Yes (incobotulinumtoxinA) | U |
| | No recommendation (rimabotulinumtoxinB, onabotulinumtoxinA and abobotulinumtoxinA) | U |
| **Which treatment strategies are useful in case of non-response to BoNT-A treatment?** | Keeping the treatment intervals constant (early detection of SNR). | U |
| | Repeated plasma exchange (contrasting NAB-induced SNR). | U |
| | Switching to BoNT-B produces only temporary benefit. | U |

BoNT, Botulinum neurotoxin; NAB, neutralizing antibodies; SNR, secondary non-responsiveness

### Are treatment intervals <12 weeks safe?

No controlled studies have compared the long-term immunogenicity of different BoNT-A.

In a consensus statement, experts recommend that reinjection is left as long as clinically possible, to minimize the chance of antibody responses. [4] The current manufacturer information suggest that the minimal interval between injections should be 10 (SPC onabotulinumtoxinA and

incobotulinumtoxinA) to 12 weeks (SPC abobotulinumtoxinA). This information, however, was based on data obtained with the original formulation of onabotulinumtoxinA, which contained a higher protein load. [70, 71] Fixed 3-month intervals may result in a decrease in treatment satisfaction toward the end of the period. Indeed up to 45% of patients indicated a preference for treatment intervals ≤10 weeks. [72]

In a trial with incobotulinumtoxinA, where injection sessions were administered at intervals of 6–20 weeks, there were no differences in the tolerability profile in the group of patients injected at 6–14 weeks with respect to the other groups. [27]

*Conclusion and recommendations*
There is only one class I study showing that, with incobotulinumtoxinA, treatment intervals <12 weeks do not increase the risk of developing antibodies. There is insufficient data to recommend or discourage the use of an interval <12 weeks for treatment with rimabotulinumtoxinB, onabotulinumtoxinA, and abobotulinumtoxinA (level U).

**Which treatment strategies are useful in case of SNR to BoNT-A treatment?**
Secondary non-responsiveness develops gradually, starting with a reduced duration of clinical effect and culminating with significant reduction of the maximal effect. [73] Therefore, constant treatment intervals and careful scoring of treatment effect may lead to an early detection of SNR. [74] However, whether an early detection is useful to prevent the development of SNR and the induction of high titers of NAB is unclear, considering the absence of effective prevention strategies.

Switching from BoNT-A to BoNT-B in patients with SNR due to NAB may initially result in effective treatment; however, most of these patients will eventually develop antibodies to BoNT-B as well. [75, 76]

Neutralizing antibodies depletion by repeated plasma exchange in one patient with SNR, allowed recovery of BoNT-A treatment effect. [77]

*Conclusion and recommendations*
It is suggested that keeping the treatment intervals constant may lead to early detection of SNR (level U).

Repeated plasma exchange is possibly effective in contrasting NAB-induced SNR (level U).

Switching to treatment with BoNT-B produces only temporary recovery of effect, often followed by development of antibodies against BoNT-B (level U).

## Management of side effects of BoNT treatment (Table 4)

**What is the most effective strategy to avoid dysphagia following BoNT treatment?**

Swallowing difficulty is caused by BoNT spreading to the throat muscles. Bilateral sternocleidomastoid injections are more frequently associated with dysphagia. [54] Dysphagia is often mild (severe in <5% of the cases), very rarely requires hospitalization or feeding tube, and disappears gradually after 2–3 weeks. [54] Dysphagia is relatively common: 7.1% of the patients reported dysphagia after treatment with the original onabotulinumtoxinA, 3.4% with the new generation onabotulinumtoxinA, 19.4% with abobotulinumtoxinA, 12.6% with incobotulinumtoxinA, and 15.6% with rimabotulinumtoxinB. [26, 44, 78] Different tendency to spread into surrounding muscles could rely on differences in formulation, size of the protein molecules, or dilution factor, although these results are based on heterogeneous studies in terms of patient selection, dose, and injected muscles. [44]

In a study, five CD patients who had reported 34 episodes of dysphagia over 98 EMG-guided injections (34.7%) were treated with additional use of ultrasounds: this resulted in no episodes of dysphagia across 27 injection sessions. [79]

*Conclusion and recommendations*

The additional use of ultrasound may lessen recurrent dysphagia after botulinum treatment (class IV, level U).

**Table 4.** Side effects and contraindications of BoNT treatment for cervical dystonia

| | | |
|---|---|---|
| **What is the most effective to avoid dysphagia?** | The additional use of ultrasound may lessen recurrent dysphagia | U |
| **What is the most effective strategy in case of neck muscles paresis?** | The use of a soft collar can relieve the symptoms of neck extensor muscles paresis. | U |
| **What is the most effective strategy to prevent injection pain?** | Skin cooling or local application of anaesthetic cream reduce injection pain | U |
| **Is BoNT treatment safe during pregnancy and lactation?** | BoNT treatment during pregnancy and lactation is not recommended and should be avoided whenever possible | U |
| **Is BoNT treatment safe for CD patients who use anticoagulants?** | The risk of hematoma following BoNT treatment by concomitant use of coumarin derivatives is low | U |
| **Is BoNT treatment safe for CD patients with concomitant neurological comorbidities?** | Patients with concomitant impairment of neuromuscular transmission may experience clinical deterioration after BoNT treatment, although in selected cases treatment might be safe and beneficial | U |

BoNT, Botulinum neurotoxin; CD, cervical dystonia.

## Contraindications for BoNT Treatment (Table 4)

**Is BoNT treatment safe during pregnancy and lactation?**

OnabotulinumtoxinA is classified as pregnancy Category C by FDA: "Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. This drug should be used during pregnancy only if the benefit outweighs the risk to the fetus." "Animal studies have provided no indications of harm during pregnancy with doses of BoNT-A normally used in clinical practice. [84]

Results of a survey on 396 doctors showed that a total of 16 pregnant women had been treated with BoNT, primarily in the first trimester. One patient (8.3%) had a miscarriage, while the other patients gave birth to healthy children after full-term pregnancies. [85] The overall risk of miscarriage, regardless of the cause, is 15–20%. [86] In the literature, up to 25 women are described who have been treated during each stage of pregnancy: two miscarriages were reported in women with previous history of miscarriage; the other cases reported uneventful pregnancy and healthy children. [87]

No studies were found on the use of BoNT during lactation. Due to insufficient data, the manufacturers do not recommend using BoNT during lactation, although it seems unlikely that BoNT may enter breast milk. [84]

*Conclusion and recommendations*

Although several cases have been reported of safe use of BoNT during pregnancy, the effect of BoNT in the unborn child has been insufficiently studied in humans; therefore, BoNT treatment during pregnancy is not recommended and should be avoided whenever possible (class IV, level U).

No studies have been conducted on the effect of BoNT on the nursing child; to exclude side effects, BoNT treatment should be avoided during lactation (class IV, level U).

**Is BoNT treatment safe for CD patients who use anticoagulants?**

No reports of complications resulting from the use of coumarin derivatives or non-vitamin K antagonist oral anticoagulants by CD patients treated with BoNT were found. According to the SPC of coumarin derivates, intramuscular injections are discouraged (but not explicitly forbidden) because of the increased risk of hematomas, while no limitation is reported for subcutaneous injections. The incidence of hematoma after BoNT injection was marginally increased in a group of 32 patients treated with phenprocoumon (3%) with respect to 32 control patients (1.8%). [88]

*Conclusion and recommendations*
The risk of hematoma following BoNT treatment by concomitant use of coumarin derivatives has not been sufficiently studied but seems low (class IV, level U).



**Is BoNT treatment safe for CD patients with concomitant neurological comorbidities?**
Treatment with BoNT may exacerbate symptoms of coexistent neuromuscular diseases [89, 90] or unmask subclinical cases. [91, 92] Myasthenia gravis, amyotrophic lateral sclerosis, and Lambert–Eaton diseases are reported as contraindications to BoNTs treatment in the respective SPCs, although cases of safe CD treatment in patients with myasthenia or amyotrophic lateral sclerosis have occasionally been reported. [93, 94]

Generalized weakness has been rarely reported after BoNT injections, most frequently in patients treated for spasticity. [95, 96]

*Conclusion and recommendations*
Patients with pre-existent impairment of neuromuscular transmission may experience clinical deterioration after BoNT treatment, although in selected cases treatment might be safe and beneficial (class IV, level U).

## GENERAL CONSIDERATIONS

Overall, there is a solid bulk of evidence supporting a good beneficial effect of the different formulations of BoNT in the treatment of CD, with a good benefit-to-risk ratio and a sustained effect over time. However, there is still room for strategies to further improve the efficacy and safety of this treatment. Robust evidence is missing concerning some practical aspects, such as treatment approaches, and the use of supportive techniques including EMG or ultrasounds. Existing knowledge often comes from secondary outcome measures in larger studies designed for other research questions. These studies often use variable methods and outcome measures, which makes comparisons difficult. Future studies should focus on these topics, by using standardized approaches and focusing on only one research question.

It has been noticed that the reported results are not always applicable to the daily practice. This may partly be due to the fact that, in the case of BoNT, optimal treatment requires some variability, according to the needs of the patients and to the progression of the symptoms. The design of future studies should also take this aspect into account.

Although the incidence of adverse events related to BoNT injections, including the formation of NAB, is low, there is a need for established strategies to prevent or manage common side effects of this treatment. To this end, multicentre collaborations are warranted in order to be able to collect an informative number of cases.

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## Supplementary material

The Supplementary material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fneur.2017.00035/full#supplementary-material.

## Conflict of interest statement

JS, YB, MR, JD, and EZ declare no conflict of interest. MC: advisory board: Medtronic and Boston Scientific. Is coinventor on a patent application relevant to deep brain stimulation? Speaking fees: Abbvie, Medtronic, Boston Scientific, and ECMT. KB: receives royalties from publication of Oxford Specialist Handbook of Parkinson's Disease and Other

Movement Disorders (Oxford University Press, 2008) and of Marsden's Book of Movement Disorders (Oxford University Press, 2012). He receives a stipend as coeditor of Movement disorders Clinical Practice journal. He received hon- oraria and/or funding for travel to speak at educational meetings/conferences from Teva–Lundbeck, Ipsen, Allergan, and Merz Pharmaceuticals. He has been paid honoraria to be on advisory board for Ipsen and Allergan companies. NG: grants and personal fees from Teva–Lundbeck, IntecPharma, and NeuroDerm; personal fees from Armon Neuromedical Ltd.\Dexel, Monfort, Pharma Two B, UCB, Novartis, Abbvie, Shaier, Genzyme, Dexel, and Sionara; grants, personal fees and other from Lysosomal Therapeutic Inc; outside the submitted work. In addition, NG has a patent concerning parkinsonian monitoring by body fixed sensors of motion and behavior pending. JK: received research and educational grants from Ipsen and Allergan. AL: speaking fee: Ipsen and Nordicinfu Care. Congress participation funded: Abbvie. MM: received speaking fees from Ipsen, Merz, Allergan, and UCB. MP: travel support from Dystonia Foundation. MS: speakers honoraria and compensations for consultations from Abbvie, Actavis, Egis, Krka, Lundbeck, Medtronic, Teva, and UCB. JF: consultancies: GlaxoSmithKline, Novartis, Teva, Lundbeck, Solvay, Abbott, BIAL, Merck-Serono, Merz, Ipsen, and Biogen. Grants: GlaxoSmithKline, Grunenthal, Fundação MSD (Portugal), Teva, MSD, Allergan, Novartis. Other: BIAL, Biogen. MV: advisory board: Merz. AA: speaker's honoraria from Ipsen, Merz, Medtronic, Boston Scientific, UCB, and Abbvie. MT: received educational grants and national DystonieNet grants from Ipsen, Allergan Pharmaceutics, Merz, Medtronic, and Actelion.

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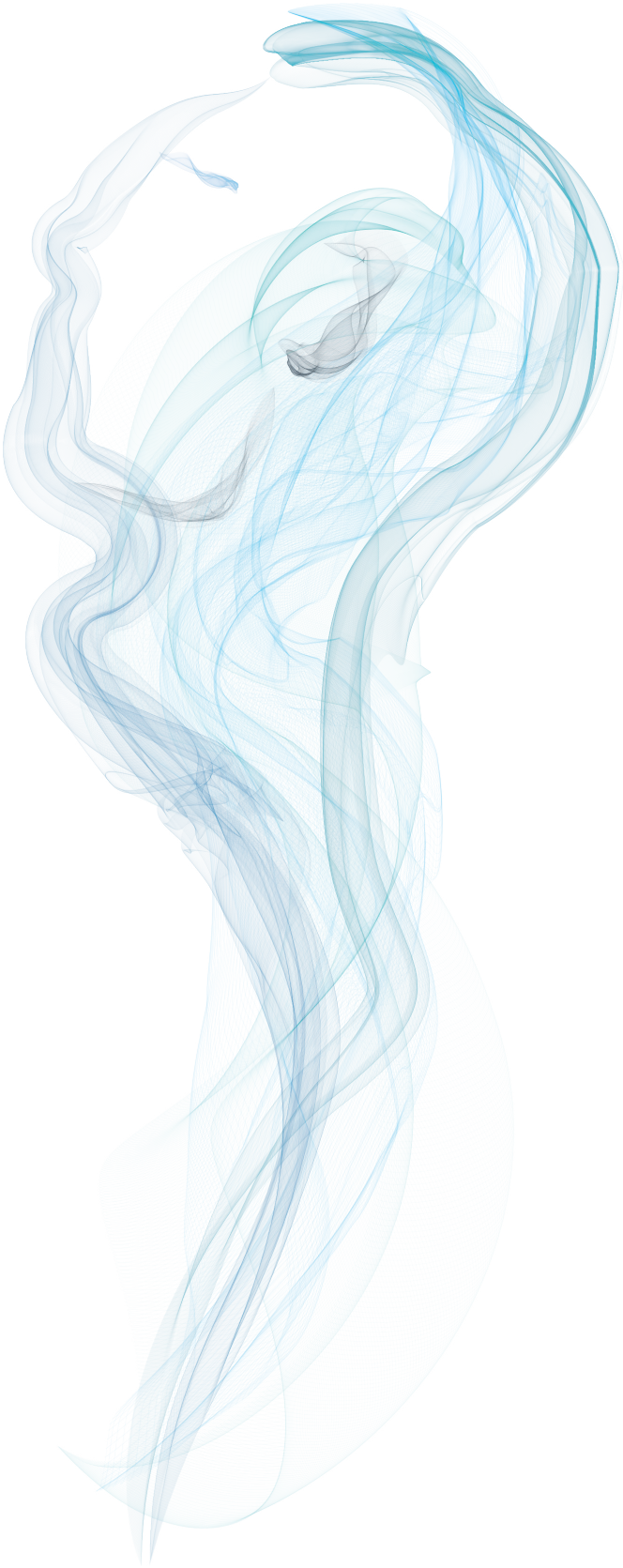

# CHAPTER 3a

## Determinants of disability in cervical dystonia

J. van den Dool, M.A.J. Tijssen, J.H.T.M. Koelman , R.H.H. Engelbert, B. Visser

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## ABSTRACT

**Background:** Cervical dystonia (CD) is characterized by involuntary muscle contractions causing abnormal postures and/or twisting movements of the head and neck. These motor symptoms can have a major impact on disability. Treatment with botulinum toxin injections aims to reduce motor symptoms, and therefore disability. Despite motor improvements, many patients still experience difficulties with performing daily life activities. To optimize treatment, other factors that determine disability should be identified.

**Objective:** To explore and identify clinical characteristics that relate to disability in CD.

**Methods:** Data on disability, severity of dystonia, anxiety, depression, pain and quality of life of 96 CD patients was analyzed with a principal component analysis (PCA). Multiple regression analysis was performed to determine which components derived from the PCA explain most of the variance in disability.

**Results:** PCA revealed five components (disability, psychiatric features, pain, physical function and severity of dystonia), explaining 74.4% of the variance in disability. Multivariate association between disability and the other components was statistically significant ($R^2$ change .433, F change (4-86) =22.39, p=.000). Psychiatric features had the largest contribution to disability (standardized beta=.555, p=.000) followed by pain (standardized beta=.232 p=.004). Physical functioning (standardized beta=.059 p=.507) and severity of dystonia (standardized beta= -.001 p=.991) had no significant contribution.

**Conclusions:** In CD patients, psychiatric features and pain are important determinants of disability. Interventions to reduce psychiatric problems and pain should have a more prominent role in the treatment of CD patients in order to improve disability levels.

# INTRODUCTION

Cervical dystonia is a neurological movement disorder characterized by involuntary muscle contractions causing abnormal postures and/or twisting movements of the head and neck. [1] These motor symptoms are the most distinctive features of CD and can have a major impact on the level of disability. Current treatments are primarily aimed at the reduction of motor symptoms. The preferred treatment is to inject the affected muscles with botulinum toxin (BTX) and is proven to be effective in reducing the involuntary movements and abnormal postures in 70-92% of the patients. [2,3] Improvement of motor symptoms also decrease the level of disability[4] but despite these improvements, many CD patients still experience difficulties with the ability to perform daily life tasks.

Disability according the World Health Organization is an umbrella term covering functions, activities and participation, as well as environmental and personal factors as defined in the international classification of functioning, disability and health (ICF).[5] Functions are the result of physiological processes and anatomical structures of the body systems. Activities are the execution of a task or action by an individual and participation is involvement in a (social) life situation. Environmental factors are the physical-, social- and attitudinal environment in which people live where personal factors include gender, age, coping styles, social background, profession and other factors that influence how disability is experienced by the individual. Thus, disability is a complex phenomenon, reflecting an interaction between these different domains. [5]

Over the last ten years there is increasing awareness that in addition to motor symptoms, non-motor symptoms may also play an important role in the management of dystonia.[6–9] A study by Klingelhoefer et al. showed that 95% of the CD patients reported non-motor features like loss of self-confidence, anxiety, depression, insomnia, fatigue and pain. [6] However, only a few studies have investigated the association of non-motor symptoms with disability, so evidence is still limited. Page et al. showed that depression and disfigurement explain 41% of the variance in disability of CD patients. [10] A study by Zetterberg et al. on the self-perceived non-motor aspects of CD indicated that self-efficacy, pain intensity, anxiety and fatigue explain much of the variance in disability in individuals with CD. [9] With evidence pointing towards the contribution of non-motor features, it is not surprising that many CD patients still encounter difficulties with the ability to perform daily life activities despite BTX treatment. Current treatments primarily aim at the reduction of motor symptoms, thus focusing mainly on the functions domain and not the domains of activity, participation, environmental factors or personal factors. Integration of treatment strategies that also focus on other domains of disability, may improve treatment outcomes.

To provide a better understanding of disability in CD patients, more research towards the association of motor and non-motor symptoms with disability is indicated. In this cross-sectional explorative study we aim to identify associations of clinical characteristics which could further unravel disability in CD.

# METHODS

## Design and participants

This cross-sectional study was performed on the baseline data of patients with idiopathic CD who participated in the Dutch DystoniaNet study that aims to optimize the BTX treatment and investigates the effectiveness of a standardized PT program in 96 patients with cervical dystonia. [11] Patients of 30 years or older and stable on BTX treatment for more than one year were recruited from the neurology departments of 15 Dutch hospitals. Participants were excluded if they had secondary or hereditary forms of dystonia, dystonia in other body parts and if they had deep brain stimulation or selective nerve denervation for the treatment of their dystonia. This project was approved by the local medical ethics committee and written informed consent was obtained from all participants.

## Data collection

Data were collected between November 2012 and June 2015 shortly before the BTX injections because we hypothesized that the effects of PT mainly occur in the period that the effects of BTX wear of. [11] Measurements were performed by one independent assessor (JvdD). In the week prior to the measurements patients filled in self-reported questionnaires. Items that were unclear or missing were discussed with the participant and filled in on the day of the measurements to minimize missing values. Both generic and disease specific instruments were used for the same variable. Generic instruments were used for comparison with other studies. Disease specific instruments were used to investigate how PT affects CD in more detail.

## Outcome measures

### Disability

Disability was measured with the disability subscale of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). The TWSTRS scale is a widely used disease specific scale in research and is a valid and reliable tool to measure severity, disability and pain in CD (Kendall Tau = 0.85, $p < 0.01$). [12–14] The disability section is a six point Likert scale consisting of six items like driving a car, reading and performing daily life activities (range 0-5). It has a maximum score of 30 points. Lower scores indicate less disability.

Disability was also measured with the Functional Disability Questionnaire (FDQ). The FDQ is a reliable disease specific scale ($r=.93$, $P<0.001$) with 27 items to measures the impact of CD on daily functioning. [15] Questions are asked about the extent to which CD affects the engagement in and performance of a sample of activities at this moment. Each item is rated on a 5-point scale (range 0-4). It has a maximum of 108 points. Lower scores indicate less disability.

**Severity of CD**

Severity of CD was measured by the severity subscale of the TWSTRS. [12–14] The TWSTRS scale is a widely used disease specific scale in research and is a valid and reliable tool to measure severity, disability and pain in CD (Kendall Tau = 0.85, $p < 0.01$). [12–14] The TWSTRS severity subscale consists of 11 items scored with a Likert scale (range 0-1 up to 0-5). It has a maximum score of 35 points where lower scores indicate less severity.

Severity of CD was also measured with the Tsui scale. [16] It is also a widely used, standardized and reliable scale (ICC=.86) to measure the severity of CD. The Tsui scale measures different aspects of abnormal posture and movements. Scores range from range 0-25 where lower scores indicate less severity of dystonia.

**Anxiety and depression**

Anxiety and depression levels were determined with the Beck's Anxiety Inventory (BAI) and Beck's Depression Inventory (BDI). [17,18] Both instruments are validated and reliable tools and are rated on a 21 item 4 point Likert scale (BDI: r = .73 with Hamilton Psychiatric Rating Scale for Depression. BAI: test-retest reliability coefficient of .67, R=.54, p=0.05 with anxiety). The maximum score of both scales is 63 points where lower scores indicate lower levels of depression and anxiety.

**Pain**

Pain was measured by the TWSTRS pain subscale. [12–14] It scores the usual level of pain, the level of pain at its worse and the level of pain at its least on an 11 point Numeric Rating Scale (NRS) (range 0-10) during the last week. In addition it scores the duration of pain and disability due to pain on a six point Likert scale (range 0-5). Al items are calculated to a total score between 0 and 20 points were lower scores indicate lower levels of pain.

Presence of pain at the present moment was rated on an 11 point NRS. A score of 0 indicates no pain and a score of 10 indicates the worst pain imaginable. The NRS is a validated and reliable tool for the assessment of pain (Spearman r =.94 between Visual Analogue Scale and NRS, test-retest reliability ICC = .90). [19,20]

**Quality of Life**

Quality of Life (QoL) was measured with the Craniocervical Dystonia Questionnaire (CDQ-24) and Short Form 36 (SF-36). [23, 24] The CDQ-24 is a validated and disease specific, self-reporting questionnaire to evaluate quality of life of patients with cervical dystonia. [21] It is divided in 5 subscales measuring stigma, emotional problems, ADL functioning, pain and social functioning. The CDQ-24 subscales showed moderate to high correlations with the SF-36 subscales (Pearson's correlation r = 0.50–0.73; P<0.001,). The score of each subscale ranges from 0 to 100 points where lower scores indicate a better QoL.

The SF-36 is a validated generic measure for QoL containing 36 items measuring eight dimensions of health namely physical functioning, role limitations due to physical functioning, bodily pain, general health perception, vitality, mental health, role limitation due to emotional functioning and social functioning. [22] Scores of the eight different dimensions range from 0 (worst) to 100 (best).

### Data analysis

Descriptive statistics (frequencies, means and standard deviations) were calculated for all variables. The Kolmogorov-Smirnov test was used to assess normal distribution of the variables.

Further statistical analysis was performed in two steps with a principal component analysis (PCA) and subsequently a multiple regression analysis. All 21 variables were first analyzed with a PCA, a widely used statistical technique to explore the underlying concepts and interrelationships among a set of variables and combine these into clusters of correlated variables (components). The variables in each component represent a common concept or process that causes the observed correlations. The advantage of using a PCA compared to the use of single outcome measures is that each component contains multiple outcome measures describing the same concept. For instance, the disability component includes information on the TWSRS disability scale, the FDQ and CDQ-24 activities of daily living scale, thus giving a better representation of that concept.

For each component continuous and discrete variables were transformed to normal distributions when appropriate and standardized into Z-scores to enable direct comparison. Reliability analyses were performed to check the internal consistency of the variables within the same component. When Cronbach's Alpha scores exceeded .7 and were internally consistent mean Z- scores for each component were calculated, which were used for the regression analysis.

To assess how much of disability could be explained by the other components of CD, values of the disability component were regressed on the values of the four other components derived from the PCA.

All statistical analyses were computed using the Statistical Packages for the Social Sciences (SPSS version 22.0).

## RESULTS

Ninety-six patients (females: 62.5%) with a mean age of 58.4 years (SD 9.2, range 38-79) and a mean disease duration of 12.7 years (SD 10.4, range 1-52 years) participated. Patient characteristics and demographics are described in Table 1, whereas baseline data for all outcome measures are displayed in Table 2.

**Table 1.** Patient characteristics and demographics (N=96)

| | |
|---|---|
| Age<br>mean (SD), range in years | 58.4 (9.2), 38-79 |
| Gender<br>male (%) – female (%) | 36 (37.5%) – 60 (62.5%) |
| Age at onset<br>mean (SD), range in years | 45.8 (10.8) 14-70 |
| Disease duration<br>mean (SD), range in years | 12.7 (10.4), 1-52 |
| Presence of dystonic head tremor<br>With tremor (%) – Without tremor (%) | 48 (50%) - 48 (50%) |



## Principal Component Analysis

PCA revealed five components, namely psychiatric features (explaining 42.1% of the variance), pain (14.1%), severity (7.5%), physical functioning (6.6%) and disability (5.5%). The components were labeled based on the variables within each component (Table 3). The component psychiatric features consisted of the variables SF-36 Mental health, SF-36 Role limitations emotional problems, SF-36 Vitality, SF-36 Social functioning, CDQ-24 Emotion, CDQ-24 Social Functioning, BDI and BAI all describing psychiatric features. The component pain consisted of the variables TWSTRS Pain, NRS, SF-36 Pain and the CDQ-24 pain scale. The component severity included the TWSTRS Severity and Tsui scale, both measuring the severity of CD. The component physical functioning consisted of the variables SF-36 Physical functioning, SF-36 Role limitations physical functioning and the SF-36 General health perceptions. The component disability included CDQ-24 Activities of daily living, CDQ-24 Stigma, FDQ and the TWSTRS Disability scale. Variables in each component showed a good internal consistency with Cronbach's alpha coefficients ranging from .775 to .934. With coefficients exceeding the recommended value of .7 all components were suitable to use in the regression analysis (see Table 4).

**Table 2.** Baseline data (N=96)

| Variable | Mean scores (SD) |
|---|---|
| Disability | |
| - TWSTRS Disability subscale | 7.3 (3.9) |
| - FDQ | 38.3 (13.4) |
| Severity of dystonia | |
| - TWSTRS Severity subscale | 16.7 (4.9) |
| - Tsui scale | 9.3 (3.3) |
| Pain | |
| - TWSTRS pain subscale | 6.7 (5.5) |
| - NRS | 3.4 (3.1) |
| Anxiety and Depression | |
| - BAI | 30.1 (8.8) |
| - BDI | 8.1 (6.5) |
| Quality of Life | |
| *SF-36* | |
| - Physical functioning | 77.7 (17.7) |
| - Role limitations physical functioning | 58.3 (41.6) |
| - Bodily pain | 60.8 (21.0) |
| - General health perceptions | 59.2 (21.0) |
| - Vitality | 60.9 (20.8) |
| - Social functioning | 74.4 (23.4) |
| - Role limitations emotional problems | 78.5 (35.2) |
| - Mental health | 73.2 (18.7) |
| CDQ-24 | |
| - Stigma | 33.5 (23.5) |
| - Emotion | 23.8 (20.3) |
| - Pain | 32.6 (23.9) |
| - Activities of daily living | 31.4 (19.7) |
| - Social functioning | 11.2 (15.3) |

Legends: TWSTRS=Toronto Western Spasmodic Rating Scale, FDQ=Functional Disability Questionnaire, NRS=Numeric Rating Scale, BAI=Beck Anxiety Inventory, BDI=Beck Depression Inventory, SF-36=Short Form-36, CDQ-24=Craniocervical Dystonia Questionnaire 24

## Predictors of disability in cervical dystonia

Multiple regression analysis was used to determine which components (psychiatric features, pain, severity of dystonia and physical functioning) contribute most to the disability component, after controlling for the influence of age, gender, disease duration. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity and multicollinearity.

The regression model explained 43% of the variance in disability and was statistically significant ($R^2$ change .433, F change (4-86) =22.39, p=.000). The component psychiatric features had the strongest unique contribution to disability (standardized beta=.555, p=.000) followed by pain (standardized beta=.232 p=.004). Physical functioning (standardized beta=.059 p=.507) and severity of dystonia (standardized beta= -.001 p=.991) had no significant contribution to the explanation of disability in this model.

**Table 3.** Pattern and Structure Matrix for PCA

| Outcome measure | Pattern coefficients | | | | | Structure coefficients | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Component 1 Psychiatric factors | Component 2 Pain | Component 3 Severity | Component 4 Physical functioning | Component 5 Disability | Component 1 Psychiatric factors | Component 2 Pain | Component 3 Severity | Component 4 Physical functioning | Component 5 Disability |
| SF-36 MH | **-.944** | .033 | -.121 | .011 | .101 | **-.889** | -.164 | -.064 | .332 | -.342 |
| SF-36 RE | **-.899** | -.018 | .182 | .100 | .224 | **.889** | .286 | .041 | -.329 | .572 |
| CDQ-24 Emotion | **.813** | .066 | .044 | .125 | .225 | **.882** | .294 | .054 | -.246 | .596 |
| BDI | **.803** | .054 | .038 | .026 | .185 | **-.843** | -.115 | .238 | .383 | -.200 |
| BAI | **.672** | -.018 | .002 | -.190 | .050 | **-.764** | -.209 | -.026 | .663 | -.381 |
| SF-36 SF | **-.650** | .020 | -.028 | .067 | -.195 | **.762** | .179 | -.020 | -.449 | .402 |
| SF-36 VI | **-.609** | .017 | -.051 | .442 | .008 | **-.760** | -.199 | -.022 | .352 | -.508 |
| CDQ-24 SF | **.586** | .011 | -.004 | .184 | .467 | **.735** | .245 | .030 | -.149 | .695 |
| TWSTRS pain | -.014 | **.996** | -.064 | .030 | -.091 | .146 | **.943** | .155 | -.143 | .205 |
| NRS | -.034 | **.975** | .049 | .164 | -.067 | .078 | **.925** | .266 | -.004 | .194 |
| SF-36 BP | -.025 | **-.661** | -.043 | .358 | -.066 | -.326 | **-.769** | -.205 | .517 | -.380 |
| CDQ-24 Pain | .015 | **.643** | .087 | -.058 | .285 | .301 | **.769** | .270 | -.263 | .522 |
| Tsui scale | .031 | .000 | **.942** | .029 | -.063 | -.046 | .198 | **.933** | .025 | .057 |
| TWSTRS severity | .013 | .009 | **.931** | .020 | -.004 | -.031 | .222 | **.932** | .007 | .112 |
| SF-36 PF | -.005 | -.003 | .060 | **.827** | -.125 | -.374 | -.197 | .038 | **.859** | -.323 |
| SF-36 RP | -.125 | .009 | -.020 | **.745** | -.153 | -.470 | -.221 | -.038 | **.827** | -.392 |
| SF-36 GH | -.419 | -.157 | .052 | **.425** | .075 | -.578 | -.296 | .037 | **.594** | -.266 |
| CDQ-24 ADL | .085 | .071 | .040 | -.155 | **.779** | .516 | .378 | .148 | -.391 | **.884** |
| FDQ | .042 | .019 | -.073 | -.271 | **.743** | .493 | .303 | .022 | -.471 | **.826** |
| CDQ-24 Stigma | .480 | .123 | -.132 | .205 | **.532** | .681 | .323 | -.059 | -.127 | **.728** |
| TWSTRS Disability | .006 | .181 | .235 | -.224 | **.456** | .329 | .427 | .333 | -.375 | **.599** |

Coefficients are measurements of the correlation between the individual outcome measure and the component. Higher numbers indicate a better fit of the outcome measure in a component. i.e. .3 or higher for pattern coefficients; .5 or higher for structure coefficients. Major pattern coefficients and structure coefficients for each outcome measure are bolded. The label of each component is based on the outcome measures with bolded coefficients.

SF-36 MH=Short form 36 Mental Health, SF-36 RE= Short Form Role limitation Emotional problems, CDQ-24 Emotion= Craniocervical Dystonia Questionnaire 24 Emotion BDI=Beck Depression Inventory, BAI= Beck Anxiety Inventory, SF-36 SF=Short Form 36 Social Functioning, SF-36 VI=Short Form 36 Vitality, CDQ-24 SF= Craniocervical Dystonia Questionnaire Social Functioning, TWSTRS pain=Toronto Western Spasmodic Torticollis Rating Scale pain, NRS=Numeric Rating Scale,SF-36 BP=Short Form 36 Bodily Pain, CDQ-24 Pain= Craniocervical Dystonia Questionnaire Pain, TWSTRS severity= Toronto Western Spasmodic Torticollis Rating Scale severity

## DISCUSSION

The results from this study suggest that the non-motor aspects psychiatric features and pain are important determinants of disability in patients with CD, showing the largest contribution to disability. Motor aspects like physical function and severity of CD seem to be of less importance since they had no significant contribution.

Increased psychiatric problems are a common feature in dystonia which have been described in numerous articles. [6–8,15,23–26] There is a growing recognition that psychiatric problems in CD patients are not merely a consequence of having a chronic condition. Psychiatric problems are not only more common in dystonia patients compared to healthy controls, but also compared to populations with other chronic disorders, suggesting they are a primary feature of the disorder. [8] Our finding of enhanced psychiatric problems are in accordance with other studies describing these problems in dystonia. However, this is one of the few studies that investigated the association of psychiatric features with disability. Zetterberg et al. showed that a non-motor model including variables like depression, anxiety, pain and self-efficacy explained 46% of the variance in disability in CD patients.[9] In our study we found similar results with a model that explained 43% of the variance in disability. Although our model also includes motor aspects like severity of dystonia and physical functioning, the component psychiatric features (which includes similar non-motor variables as Zetterberg's model) appeared to be the most important predictor of disability.

Pain also has an important contribution to the explanation of disability. This finding was similar to other studies in CD. [9,27–29] Werle et al. reported that 84.3% of the patients experienced pain and that pain is a major source of disability in 17% of the patients. [29] However, in this study measurements were performed just prior to the BTX injections. At this point BTX effects have worn off and severity of dystonia and pain levels are at their worst. If measurements were performed at a time with better BTX effects, pain might have contributed less to the explanation of disability.

Physical functioning had no significant contribution to the explanation of disability in CD. This was an unexpected finding since many patients report disability due to physical impairments. [23] Our finding may be explained by the correlations between the individual variables and the components psychiatric features factors and physical functioning (Table 3 Structure coefficients). Outcome measures having high correlations with psychiatric features also have medium to high correlations with physical functioning. The BAI for instance has high correlations of -.764 on psychiatric features and .663 on physical functioning. These correlations indicate that there is a lot of shared variance between the components. The regression analysis based on these components however, only shows the unique variance of each component. Shared variance was statistically removed by SPSS with both components in the same model. The effect of physical functioning is therefore possibly masked by the effect of psychiatric features. The effect of physical functioning on disability remains unclear for this reason and should be further investigated.

Severity of CD made no significant contribution to the levels of disability. Disability has a multi-dimensional character covering the domains as described by the ICF model.[5] Severity of CD only covers the domain of functions while other aspects like someone's ability to cope with physical, social or mental challenges (domains of activities, participation and personal factors) also play an important role in the level of disability. [30] Individuals with severe dystonia sometimes report low levels of disability while individuals with milder symptoms report high levels of disability. However, conflicting data exists on the relation between severity and disability. Werle et al. found that greater severity was related to higher levels of disability so the results from this study need to be replicated to verify our findings. [29]



### Limitations

All outcome measures except the Tsui scale and TWSTRS were self-reported questionnaires. Although there are no alternatives to measure concepts like pain, anxiety, depression or QoL than with self-reported questionnaires, there is a possible risk of response bias which can lead to an over- or underestimation of the outcomes.

Another limitation of our study that we collected the data just prior to the BTX injections when the BTX effects have worn off and severity of dystonia and pain levels are at their worst.

At the peak effect of BTX, pain might have contributed less to the explanation of disability. It is therefore not clear how generalizable the association of pain is to the overall experience of patients with CD who are treated with BTX. It is of interest that the motor severity prior to the botulinum toxin injection is also at its worst and still not an important factor on disability.

The results of this study suggest that psychiatric features and pain are important determinants of disability. Interventions aimed at reducing psychiatric problems and pain should therefore have a more prominent role in the rehabilitation of CD patients to improve treatment outcomes. This implies a multidisciplinary approach aimed at reducing problems in all the domains of disability (functions, activities, participation, environmental and personal factors) to optimize treatment outcomes.

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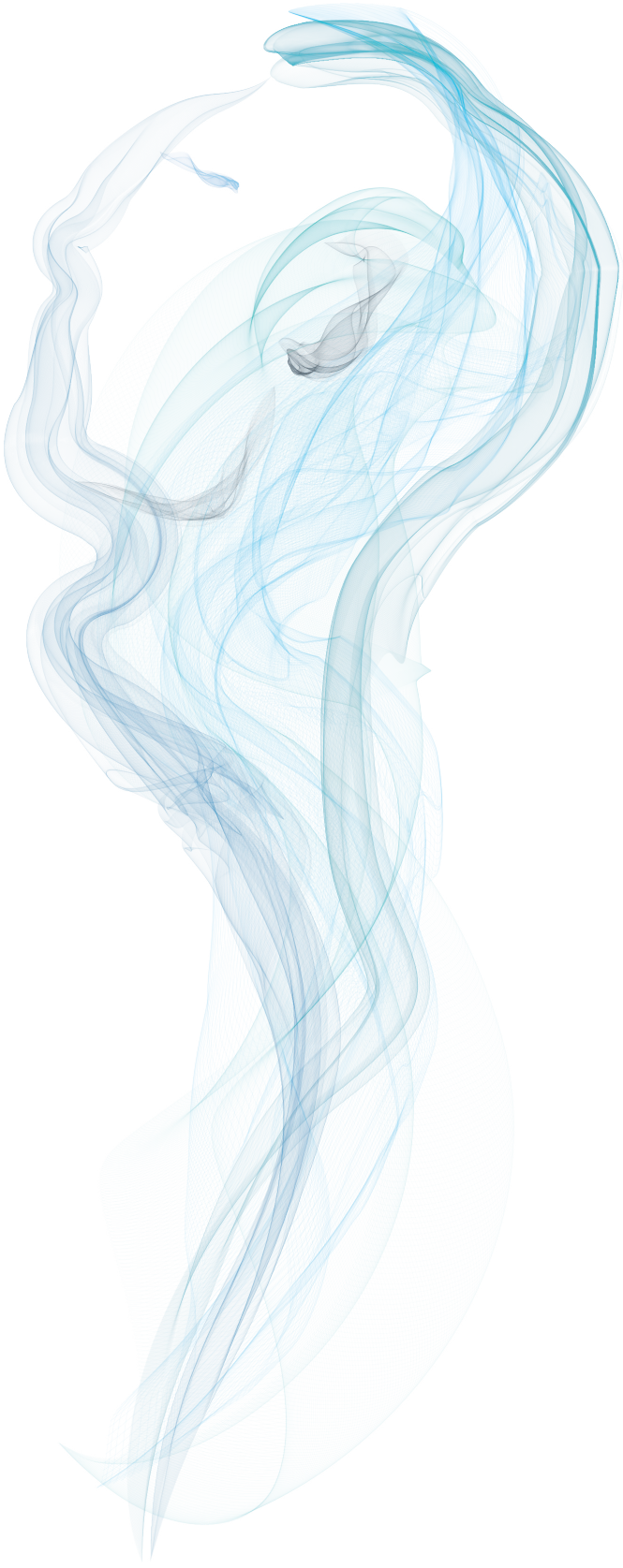

# CHAPTER 3b

## Driving performance in cervical dystonia

J. van den Dool, B. Visser , R.B. Huitema, S.R. Caljouw, M.A.J. Tijssen

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## ABSTRACT

**Objective:** To explore driving performance and driving safety in patients with cervical dystonia (CD) on a simulated lane tracking, intersections and highway ride and to compare it to healthy controls.

**Design:** This study was performed as an explorative between group comparison.

**Participants:** Ten CD patients with primary CD, 30 years or older, stable on botulinum toxin treatment for over a year, holding a valid drivers' license and being an active driver were compared with ten healthy controls, matched for age and gender.

**Main outcome measures:** Driving performance and safety, measured by various outcomes from the simulator, such as the standard deviation of the lateral position on the road, rule violations, percentage of line crossings, gap distance and number of collisions. Fatigue and driving effort were measured with the Borg CR-10 scale and self-perceived fitness to drive was assessed with Fitness to Drive Screening.

**Results:** Except for a higher percentage of line crossings on the right side of the road by controls (median percentage 2.30, range.00-37.00 vs .00, range .00-9.20, p=.043), no differences were found in driving performance and driving safety during the simulator rides. Fatigue levels were significantly higher in CD patients just before (p=.005) and after (p=.033) the lane tracking ride (patients median fatigue levels before 1.5 (range 0.00 to 6.00) and after 1.5 (range 0.00 to 7.00) vs controls median fatigue levels before and after 0.00 (no range). No significant differences were found on self-perceived fitness to drive.

**Conclusion:** In patients with CD there were no indications that driving performance or driving safety were significant different from healthy controls in a simulator. Patients reported higher levels of fatigue both before and after driving compared to controls in accordance with the non-motor symptoms known in CD.

# INTRODUCTION

Cervical Dystonia (CD) is a neurological disorder characterized by involuntary muscle contractions causing abnormal positions and involuntary movements of the neck and head. With an estimated prevalence of 4.9 (CI95% 3.6 to 6.9) patients per 100.000 persons, it is the most common form of dystonia. [1] Besides motor symptoms, patients may also suffer from non-motor symptoms including pain, anxiety, depression, fatigue, and loss of self-confidence. [2,3] Both motor and non-motor symptoms can have a major impact on the level of disability causing limitations in daily life activities. [4, 5] The preferred treatment is to inject the affected neck muscles with Botulinum Toxin (BoNT) injections which reduces involuntary movements and abnormal postures in 75-92% of the patients. [6] Improvement of motor symptoms also decrease the level of disability but BoNT treatment is often not fully satisfactory and many patients still maintain difficulties while performing daily life tasks.



The ability to drive a vehicle is a very important part of daily life activities. It is important for social contacts, to get to work, and to access everyday needs such as goods and services. Driving a motor vehicle is a complex task requiring adequate interaction between visual, cognitive and motor skills. It is known that a wide range of acute and chronic medical conditions may impair driving performance and safety. [7] Since CD is characterized by involuntary movements and/or abnormal postures of the neck, patients may be impaired in visual scanning of the environment which may affect driving performance. In clinical practice some patients with CD indicate to use tricks or operational adaptations in the car, such as supporting their head while driving or turning their entire torso to the required direction before crossing an intersection. It is conceivable that patients also apply compensatory actions on a tactical level during driving, such as lowering speed or keeping appropriate distance. Furthermore, patients might compensate on a strategic level for example by adequate planning of a trip, avoiding rush hours or using automatic gear shift. [8] The known fatigue problems in CD patients can also hamper their driving abilities.[9] Currently there is no literature available on driving performance in CD.

A safe and standardized objective method to determine driving performance is with a driving simulator which enables to study real time driving performance and driving strategies in a controlled environment. [7,10] Driving performance is a concept that refers to the ability of a person to safely navigate a driving vehicle through traffic and can vary for different traffic situations. It can be measured by different outcomes such as vehicle control, speed adaptations to different traffic situations, distance control between the driver and other traffic or gap acceptance time for crossing intersections or merging onto adjacent lanes. A subjective judgement of a participant's driving performance is the self-reporting questionnaire Fitness To Drive Screening (FTDS or previously called the Safe Driving Behaviour Measure). Based on the indications by patients in the clinical practice and the limitations in performing daily life activities, it is hypothesized that the operational driving skills are impaired and that CD patients have more difficulties in controlling the

vehicle. To compensate for these impairments patients, when compared to healthy controls, might drive more carefully by lowering their speed, keeping more distance to a car in front or selecting a larger gap between approaching cars when crossing an intersection. It is also hypothesized that patients experience more fatigue and have to make more effort to drive safely compared to healthy controls. The main goal of this pilot study was therefore, to explore objective driving performance and the subjective driving evaluation (measured by the FTDS) in a small group of persons with CD and to compare it to healthy controls.

# METHODS

## Study design

The study was performed as an explorative between group comparison.

## Participants

Ten CD patients were recruited from the neurology department of the University Medical Center Groningen with the following inclusion criteria: primary CD, 30 years or older, stable on BoNT treatment for over a year, holding a valid drivers' license and being an active driver. Participants were excluded if they had secondary or hereditary forms of dystonia, dystonia in other body parts than the neck, if they had had deep brain stimulation or selective nerve denervation for the treatment of their dystonia or suffered from other neck conditions. Healthy controls, matched for age and gender, holding a valid drivers' license and active drivers were recruited among hospital staff and their relatives. Eligible participants had to understand the spoken and written Dutch language. Written informed consent was obtained from all participants. This study was approved by the local medical ethics committee (METC number 2013/507).

## Procedures

### Data collection

Measurements were performed four to eight weeks after BoNT injections. With an average working period of 12 weeks and a peak effect between two to six weeks after injections, we expected an average effect of the BoNT injections. [12]

The main parameters, driving performance and driving safety, were derived from a validated fixed based driving simulator located at the University Medical Center Groningen (ST Software Simulator Systems).[12] The simulator consisted of a projection screen stage and an open cabin mock-up standing within this stage and containing a force-feedback steering wheel, accelerator, clutch, brake pedals and audio sound simulated driving sound. The projection screen stage held three video projectors and three large flat-screens of 4.5 m length, bent 60 degrees inwards, which presented the participants with a 180 degrees horizontal view. Front and side windows as well as a

rear view mirror and side mirrors were projected onto the screen. The simulator software rendered virtual road environments simulating real world road environments and traffic situations. Data of all relevant parameters were recorded at a rate of 10Hz. Data was processed and stored in binary data files which were exported to SPSS 24.0 for further analysis.

**Driving tasks in the simulator**

Participants performed three types of rides to assess various aspects of driving performance; a lane tracking ride, an intersection ride, and a merging ride. Shifting was automatically controlled in all rides. Each ride was performed twice, with the first ride to get the participants familiarized with the simulator and traffic situations. Data from the second rides were used for the analysis.



The lane tracking practice ride was in a rural area on a road with alternating left-right curves of 40 degrees and 500m radius and a continuous stream of traffic from the opposing direction but no traffic on the lane of the simulator driver. The speed was regulated by the computer and increased stepwise from 50 km/h up to 100 km/h. The test ride was similar to the practice ride with the difference that participants had to control the speed their selves. First participants had to drive with a comfortable speed after which they were asked to drive as if they were in a hurry.

During the intersection rides subjects were confronted with six intersections with different regulations of right-of-way. Participants were always driving straight ahead on the intersections. Speed limits on traffic signs varied between 60 and 80 km/h and participants were asked to apply general traffic rules.

The first and sixth intersections were unmarked with traffic coming from the right and left. In the Netherlands, cars drive on the right side of the road and traffic coming from the right has right of way. The second intersection was also unmarked with traffic only coming from the right so the participant had to give way. The third intersection was unmarked with traffic coming from the left so the participants had right of way. The fourth intersection was marked with a traffic light and participants could continue driving when it turned green. The fifth intersection was marked with a give way sign with traffic coming from the right and left. After the fifth intersection an unexpected event occurred. A parked car pulled out of the parking lot onto the drive way so the participants had to break to avoid a collision. For the analyses intersections 1, 2, 5 and 6 were selected in which subjects had to determine when it was safe to cross (gap distance) by observing the environment in various directions requiring (a combination of) head movements, trunk movements and eye movements.

The last ride was a merging ride. First subjects needed to merge on the right lane of a highway. Subsequently they had to overtake a car where after they had to return to the right lane. Finally they had to leave the highway and park the car at the side of the road.

Driving in a simulator can provoke motion sickness. Participants were instructed to indicate if they were feeling sick during the driving tasks. If symptoms such as dizziness or nausea were reported or observed, participants were advised to take a break and if symptoms did not reduce to abort the driving simulation.

## Outcome measures

### Patient-related outcomes

The Tsui scale was used to determine the severity of dystonia. [13] The Tsui scale measures different aspects of abnormal posture and movement in CD patients. It has a max score of 25 point where higher scores indicate higher levels of severity.

Perceived muscle fatigue in the neck area and driving effort was rated just after the start and just before the end of the simulated drive in order to determine the effects of drive duration on driving performance, using the Borg CR-10 scale.[14] The Borg CR-10 scale is a reliable and validated scale 11 point rating scale, ranging from 0 to 10 on which perceived fatigue and driving effort during the performance of a task can be monitored. For perceived fatigue a score of 0 means that a patient has no muscle fatigue or discomfort in the neck area at all and a score of 10 means there is very much muscle fatigue or discomfort in the neck area. In driving effort a score of 0 means that driving does not require any effort while a score of 10 means that it requires very much effort.

### Fitness To Drive Screening questionnaire

Self-perceived fitness to drive was measured with the Fitness To Drive Screening questionnaire (FTDS). The FTDS questionnaire (formerly known as the Safe Driving Behaviour Measure) is a self-report questionnaire related to driving fitness, driving behaviour and driving safety with a good reliability (ICC .253, $p < .001$).[11,15] The FTDS has three sections: Section A, Demographics or general information about the driver; Section B, Driving history profile; and Section C, Ratings of driving difficulty pertaining to 54 driving skills. Difficulty of the driving task was rated with a 5-point Likert scale (ranging from 1= extremely difficult to 5 = not difficult at all). A mean score was calculated for each individual by summing up all scores divided by the number of items endorsed.

## Simulator outcomes

### Lane tracking ride

The main measure to assess driving performance in the lane tracking ride was the standard deviation of lateral position (SDLP). The SDLP is the primary outcome for vehicle control and measures the weaving of a car during driving. [16] SDLP is considered as the golden standard of driving performance in driving simulators with high test–retest reliability.[16]

The SDLP was assessed twice, once for the speed of choice section (SDLP choice) and once for

the section participants were asked to drive in a hurry (SDLP hurry). Additional outcomes were average speed, the number of collisions and percentage of line crossings on either side of the road during each ride.

**Intersections ride**

The main outcome to measures driving performance in the intersection ride were gap distance left and right. Gap distance left and right is defined as the shortest distance from an approaching car coming from the left or right measured in meters. The shorter the distance between the approaching car and the subject, the more risk he or she took to cross the intersection. This also applied for traffic coming from the left which has to give right of way in the Netherlands on unmarked intersections. Traffic coming from the left was programmed to stop to let the subject pass. However, it was also programmed to continue to drive if a subject waited too long.



Additional outcomes on the intersections ride were the lowest speed when approaching the intersection, average deviation from the speed limit and the number of collisions.

**Merging**

In the merging ride the main parameter to measure driving performance was deceleration of the rear car. Deceleration of the rear car was defined by how fast the car behind the participant had to break once a subject merged on the adjacent lane. Deceleration of the rear car depended on distance between the merging and rear car, absolute speed of the rear car and differential speed between the merging and rear car. A larger deceleration of the rear car can be interpreted as a larger risk being taken by the merging car.

Additional outcomes on the merging ride were the speed while merging and rear time headway. Rear time headway was the distance measured in seconds between the subject and car behind the subject once merged on to the adjacent lane. The smaller the time to headway the more risk a participant took to merge.

## Statistical analysis

First, descriptive statistics (frequencies, means and standard deviations) for patient characteristics were calculated. A Kolmogorov-Smirnov test was used to assess normal distribution of the variables.

Based on the small sample size and unevenly distributed data a Mann-Whitney U was performed to determine differences on simulator outcomes and self-perceived fitness to drive between the patient and control group. To determine the changes in fatigue of the subjects within each group during the driving tasks, a Wilcoxon Signed rank test was used.

# RESULTS

## Participants

A total of 11 patients and 14 controls were included. However, one patient and four controls had to stop the simulator drives due to motion sickness and were excluded from further analysis.

Mean age of the remaining 10 CD patients (5 females, 5 males) had a mean age of 56.8 years (SD 7.7, range 47-69) and a mean disease duration of 15.1 years (SD 11.7, range 1-36 years). Patients showed an average score of 9.7 (SD, 3.1, range 5-14) for the severity of dystonia as measured with the Tsui scale. The control group existed of 10 persons (5 females, 5 males) with a mean age of 57.3 years (SD 7.4, range 48-67) which were matched for age and gender. Characteristics for each group are described in Table 1.

**Table 1.** Participant characteristics

| | Patients (n=10) | Controls (n=10) |
|---|---|---|
| **Age**<br>**Mean (SD, range)** | 56.8 (7.7, 47-69) | 57.3 (7.4, 48-67) |
| **Gender M/F** | 5/5 | 5/5 |
| **Severity of dystonia (Tsui Scale)**<br>**Mean (SD, range)** | 9.7 (3.1, 5-14) | NA |
| **Disease duration in years**<br>**Mean (SD, range)** | 15.1 (11.7, 1-36) | NA |
| **Driving experience in years**<br>**Mean (SD, range)** | 37.5 (9.3, 25-51) | 37.4 (8.9, 25-49) |
| **Driving experience in km/yr**<br>**Range (number of participants)** | <1000 (2)<br>1000-5000 (4)<br>5000-10000 (3)<br>10000-50000 (1)<br>>50000 (0) | <1000 (0)<br>1000-5000 (3)<br>5000-10000(3)<br>10000-50000 (2)<br>>50000 (1) |
| **Car accidents in last year** | 0* | 0* |
| **Traffic fines in last year**<br>**Total (range)** | 1 (0-1) | 10 (0-3)* |

NA= Not Applicable
* For 9 out of 10 cases because one did not report the information

## Simulator rides

On the speed of choice section of the lane tracking ride, no significant differences were found on the SDLP. Patients showed a median SDLP of 27.60 cm (range 15.80 to 35.70) compared to 25.90 cm (range 21.30 to 43.00) in controls (p=.853). None of the other outcomes, except the percentage of line crossings on the right side of the road, showed significant differences either. Healthy controls had a significant higher percentage of line crossings than patients. Patients had a median of .00

(range .00-9.20) percent of the time that they crossed the line compared to a median of 2.30 (range .00-37.00) percent of the time in controls (p=.043). There were no line crossing at the left side of the road.

On the speed in hurry section of the lane tracking ride, none of the outcomes showed significant differences. Patients showed a median SDLP of 28.40 cm (range 20.30 to 39.70) versus 31.50 cm (range 21.10 to 37.80) for healthy controls (p=.684). An overview of median scores and ranges for all the outcomes and the between group differences are displayed in Table 2.

On the intersections ride no significant differences were found on any of the outcomes. On intersection 1 median gap distance with traffic from the left was 2.78 meters (range 1.00 to 174.44) for patients versus 1.29 meters ( range 1.00 to 164.00) for controls (p=1.000). Median gap distance with traffic from the right was 90.64 meters (range 3.15 to 107.23) for patients and 72.84 meters (range 5.07 to 123.85) for controls (p=.226). On intersection 2 traffic was only coming from the right. Patients showed a median distance of 191.66 meters (range 16.29 to 291.78) and controls 93.92 meters (range 7.19 to 218.66)(p=.602). On intersection 5 traffic was coming from the left and right where subjects had to give right of way. The majority of the subjects waited until all traffic had passed before crossing the intersection. Eight patients and eight controls waited until all the traffic from the left had passed before crossing the intersection. Nine patients and nine controls waited until all the traffic from the right had passed. Gap distance and statistical differences between the groups could not be calculated for these subjects because there was no gap distance since all the approaching cars had already passed. For these participants gap distance was recorded as a missing value. On intersection 6 median gap distance with traffic from the left was 1.00 meters (range .99 to 8.00) for patients versus 1.00 meters (range 1.00 to 153.65) for controls (p=.741). Median gap distance with traffic from the right was 101.92 meters (range 2.40 to 110.67) for patients and 98.01 meters (range 16.97 to 138.11) for controls (p=.650).

It was noticeable however that both patients and controls drove with speeds well under the speed limit on the sections where a speed of 80 km/h was allowed (patients median speed -6.99km/h (range -31.23-8.21) and controls median speed -8.75 km/h ( range -20.83-.92), p=.734).

On the merging ride no significant differences were found on the primary outcome deceleration of the rear car, nor on any of the other additional outcomes. Median deceleration of the rear cars was .00 for both patients and controls during merging on the highway (range .00 to .10 for patients vs range -.20 to .00 for controls, p=.169). During overtaking rear cars had to decelerate with a median of 4.30 km/h for patients (range -6.70 to -.80) and for controls with a median of -5.30 km/h (range -8.00 to -4.00, p=.216).

## Self-perceived fatigue and driving effort

For self-perceived fatigue, patients showed a median fatigue score of 1.5 at the start of the lane tracking (range=.00 to 6.00) and also 1.5 after finishing (range=.00 to 7.00). For controls a median score of .00 was found at the start (range=.00 to .00) and a median score of .00 after finishing the ride (range=.00 to 5.00). Differences were significantly higher for patients at the start (p=.005) and finish (p=.033) of the lane tracking ride, indicating higher levels of fatigue. None of the other rides showed significant differences between the groups on self-perceived fatigue. Neither the patient nor control group showed significant differences in change scores of fatigue before and after each driving task

A between comparison of the differences between self-perceived fatigue before and after each driving task also did not reveal significant differences on any of the simulator drives.

On the Borg scale for driving effort no significant differences for between the group comparisons, nor for within group comparisons were found for any of the simulator rides. An overview of median scores, ranges, between group differences and within group differences for self-perceived fatigue and driving effort are displayed in table 3.

## Self-perceived fitness to drive

Self-perceived fitness to drive showed a median of individual mean FTDS scores of.33 (range .01 to .96) for patients and .21 for controls (range .00 to .74). Group comparison of FTDS scores revealed no significant difference (p=.178). An overview of median scores, ranges and the between group differences for the FTDS are displayed in table 3.

**Table 2.** Median scores, ranges and between group difference for driving performance and driving safety

| Outcome | Patients (N=10) Median (range) | Control (N=10) Median (range) | Between group difference (p-value) |
|---|---|---|---|
| **Lane tracking ride** | | | |
| *Speed of choice* | | | |
| SDLP in cm | 27.60 (15.80-35.70) | 25.90 (21.30-43.00) | .853 |
| % line crossings | | | |
| - Left | .00 (.00-.30) | .00 (.00-.00) | .739 |
| - Right | .00 (.00-9.20) | 2.30 (00-37.00) | .043* |
| Nr. of collisions | 0 | 0 | NA |
| Average speed in km/h | 79.45 (55.60-86.60) | 73.20 (58.00-82.10) | .280 |
| *Speed in hurry* | | | |
| SDLP in cm | 28.40 (20.30-39.70) | 31.50 (21.10-37.80) | .684 |
| % line crossings | | | |
| - Left | .00 (.00-.60) | .00 (.00-.00) | .739 |
| - Right | .00 (.00-10.20) | .70 (.00-16.20) | .280 |
| Nr. of collisions | 0 | 0 | NA |
| Average speed in km/h | 91.05 (62.90-101.30) | 88.60 (74.90-99.70) | .481 |
| **Intersections ride** | | | |
| Gap left int 1 in meters | 2.78 (1.00-178.44) | 1.29 (1.00-164.00) | 1.000 |
| Gap left int 2 in meters | NA | NA | NA |
| Gap left int 5 in meters[a] | NA | NA | NA |
| Gap left int 6 in meters | 1.00 (.99-8.00) | 1.00 (1.00-153.65) | .741 |
| Gap right int 1 in meters | 90.64 (3.15-107.23) | 72.84 (5.07-123.85) | .226 |
| Gap right int 2 in meters[b] | 191.66 (16.29-291.78) | 93.92 (7.91-218.66) | .602 |
| Gap right int 5 in meters[c] | NA | NA | NA |
| Gap right int 6 in meters | 101.92(2.40-110.67) | 98.01 (16.97-138.11) | .650 |
| Minimum speed int 1 in km/h | .00 (.00-7.57) | 6.00 (.00-25.49) | .084 |
| Minimum speed int 2 in km/h | 5.17 (1.00-7.79) | 4.84 (.76-7.48) | .806 |
| Minimum speed int 5 in km/h | .00 (.00-.83) | .00 (.00-.00) | .168 |
| Minimum speed int 6 in km/h | 2.73 (.00-6.78) | 6.90 (.00-8.17) | .070 |
| Deviation from speed limit 60 km/h | 1.02 (-5.01-12.81) | 2.39 (-5.21-17.26) | .791 |
| Deviation from speed limit 80 km/h | -6.99 (-31.23-8.21) | -8.75 (-20.83-.92) | .734 |
| Nr. of collisions | 0 | 0 | NA |
| **Merging ride on highway** | | | |
| *Merging* | | | |
| Deceleration rear car merging in km/h | .00 (.00-.10) | .00(-.20-.00) | .169 |
| Speed while merging in km/h | 92.50 (88.00-100.70) | 97.50 (85.00-111.20) | .566 |
| Rear time to headway merging in sec | 1.40 (.20-2.40) | 1.50 (.20-2.20) | .965 |
| *Overtaking* | | | |
| Deceleration rear car overtaking in km/h | -4.30 (-6.70 to -.80) | -5.30(-8.00 to -4.00) | .216 |
| Speed while overtaking in km/h | 98.60 (91.50-103.00) | 95.60 (91.60-99.70) | .566 |
| Rear time to headway overtaking in sec | .70 (.40-1.00) | .80 (.20-.90) | .559 |
| Minimum time headway overall in sec | .20(.13-.33) | .28 (.10-.42) | .185 |

Legend: SDLP= Standard Deviation of the Lateral Position on the road. NA= Not Applicable
* =significant at the P<.05 level.
[a]= Eight patients and eight controls waited until all oncoming traffic passed before crossing the intersection so gap distance and statistical difference could not be calculated.
[b]= Medians, ranges and significance are based on data from 5 patients and 5 controls. Remaining participants waited until all oncoming traffic passed before crossing the intersection so gap distance could not be calculated.
[c]=Nine patients and nine controls waited until all oncoming traffic passed before crossing the intersection so gap distance and statistical difference could not be calculated.

**Table 3.** Median scores and median change scores of the Borg perceived fatigue, Borg driving effort and FTDS

| Outcome | Patient Median (range) | Control Median (range) | Between group difference (p-value) | Within group difference (p-value) |
|---|---|---|---|---|
| **Lane tracking ride** | | | | |
| Borg perceived fatigue | | | | |
| • Start of the ride (range) | 1.5 (0-6) | 0 (0-0) | .005* | Patients: .593 |
| • Finish (range) | 1.5 (0-7) | 0 (0-5) | .033* | Controls: .317 |
| • Change score (range) | 0 (-3-6) | 0 (0-5) | .957 | |
| Borg driving effort | | | | |
| • Just after start (range) | 1 (0-6) | 2.5 (0-7) | .377 | Patients: .892 |
| • Just before finish (range) | 1 (0-7) | 2.5 (0-7) | .419 | Controls: 1.000 |
| • Change score (range) | 0 (-3-6) | 0 (0-0) | .619 | |
| **Intersections ride** | | | | |
| Borg perceived fatigue | | | | |
| · Start of the ride (range) | 1 (0-5) | 0 (0-6) | .051 | Patients: .257 |
| · Finish (range) | 2 (0-6) | 0 (0-6) | .095 | Controls: .317 |
| · Change score (range) | 0(-1-4) | 0 (0-2) | .619 | |
| Borg driving effort | | | | |
| · Just after start (range) | 2.5 (0-7) | 4 (0-8) | .515 | Patients: .317 |
| · Just before finish (range) | 2.5 (0-8) | 4 (0-8) | .492 | Controls: 1.000 |
| · Change score (range) | 0 (-1-1) | 0 (0-0) | .278 | |
| **Merging ride on Highway** | | | | |
| Borg perceived fatigue | | | | |
| • Start of the ride (range) | 1 (0-4) | 0 (0-5) | .400 | Patients: .655 |
| • Finish (range) | 1 (0-5) | 0 (0-5) | .220 | Controls: .317 |
| • Change score (range) | 0 (-1-4) | 0 (-3-0) | .563 | |
| Borg driving effort | | | | |
| • Just after start (range) | 1 (0-5) | 2 (0-8) | .332 | Patients: 1.000 |
| • Just before finish (range) | 1 (0-5) | 2 (0-8) | .332 | Controls: 1.000 |
| • Change score (range) | 0-(0-0) | 0 (0-0) | 1.000 | |
| FTDS (range) | .33 (.01-.96) | .21 (.00-.74) | .178 | |

Legend: FTDS=Fitness To Drive Screening
* =significant at the P<.05 level.

## DISCUSSION

In this explorative pilot study, patients with CD did not show significant differences in driving performance as measured with the SDLP on the lane tracking ride, gap distance on the intersections ride and deceleration of the rear car on the merging ride compared to controls. On intersection 5, where the participants had to give way, all but two patients and two controls waited until all approaching traffic had passed before crossing the intersection. Therefore no gap distance and statistical differences between the groups could be calculated. However, this finding indicates that both patients and controls took no risk with crossing the intersection.

On the additional outcomes, the percentage of line crossings on the right side of the road was significantly higher in healthy controls in the first lane tracking ride, but no differences in line crossings were found between groups in any of the following rides. Self-perceived fatigue was significantly higher for patients compared to controls at the start and finish of the lane tracking ride, but this group difference was not significant in the other driving tasks. No differences between the groups were found in self-perceived fitness to drive.

It was remarkable that no significant differences were found in driving performance in the simulator between the groups, since many patients indicate having trouble with different practical aspects of driving. Patients indicated that they use tricks while driving in their car such as supporting their head while driving or turning their entire torso to oversee oncoming traffic before crossing an intersection. It was hypothesized that patients would compensate for their physical limitations by driving more carefully and slowly. Studies on compensatory driving behaviour indicate that elderly and neurological patients tactically compensate for their limitations by driving slower, increasing the distance to the car in front, waiting longer at intersections, and selecting larger time gaps between the passing cars for merging. [13,18–20] These adaptations in driving behaviour were not observed in the present experiment.



A possible explanation for not finding significant differences on these outcomes is that measurements were performed four to eight weeks after BoNT injections. With an average working period of 12 weeks and a peak effect between two to four weeks after injections, we expected an average effect of the BoNT injections. BoNT injections are the treatment of choice in CD, and most patients respond well to treatment which decreases dystonic activity. [6] Therefore patients did not have to compensate for the dystonic movements as much and might not have experienced sufficient functional limitations to apply compensatory behaviour.

Another possible explanation for not finding significant differences is that CD patients have good coping strategies. CD patients may compensate for impaired control of head movements by moving their eyes or torso instead of their heads while looking for oncoming traffic. Future studies should therefor integrate methods to measure eye movements, gaze behavior and head movements with the simulator rides to test this hypothesis. Furthermore, the simulator rides were relatively short. This study did not investigate driving performance with prolonged driving, which patients with CD report as problematic. Therefore, the simulator rides were possibly too short to provoke any differences between the groups.

We did find significant differences between groups in fatigue at the start and end of the lane tracking ride. These findings are in line with a study by Smit et al. [3] that showed significant higher levels of fatigue in CD patients measured with the Fatigue Severity Scale compared to health controls. Fatigue, however, did not increase significantly more during the simulator drives in CD patients compared to healthy controls.

The effects of BoNT therapy could explain why there was no significant increase in fatigue during the driving tasks. Due to the decreased dystonic activity in the affected muscles, patients might not have had to compensate for the dystonic movements as much and did not experience a significant increase in fatigue during the driving tasks.

Because this study was an explorative pilot study, there were some limitations.

First of all, the sample size was small so no firm conclusions can be made based on the findings in this study. Secondly, the simulator rides were relatively short and no measures for head or eye movement and gaze direction were incorporated meaning that compensations on this level could not be recorded.

In conclusion, this study compared driving performance between patients with CD and healthy controls on a lane tracking ride, an intersections ride and a merging ride on a highway with a driving simulator. No indications were found that driving performance was significantly different in CD patients compared to healthy controls. However, future studies with larger groups and longer simulator scenarios in which head and eye trackers are applied should be performed to investigate whether these findings can be replicated and to what extent patients compensate for impaired control of head movement.

## CONFLICT OF INTEREST STATEMENT

MAJ Tijssen received unrestricted grants from Ipsen Pharmaceutical and Allergan Inc. for studies, teaching workshops on dystonia, and to finance a specialized dystonia nurse. Neither Ipsen nor Allergan had a role in the study design, collection, analysis, interpretation of data, in the writing of the report, or in the decision to submit the paper for publication. The other authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

J. van den Dool contributed to the study design, data collection, data analysis, data interpretation, figures and writing of the manuscript. B. Visser contributed to the study design, data collection, data analysis, data interpretation, figures and writing of the manuscript. R.B. Huitema contributed to the study design, data collection, data interpretation and writing of the manuscript.

S.R. Caljouw contributed to the study design, data analysis, data interpretation and writing of the manuscript. M.A.J. Tijssen contributed to the study design, data collection, data analysis, data interpretation and writing of the manuscript.

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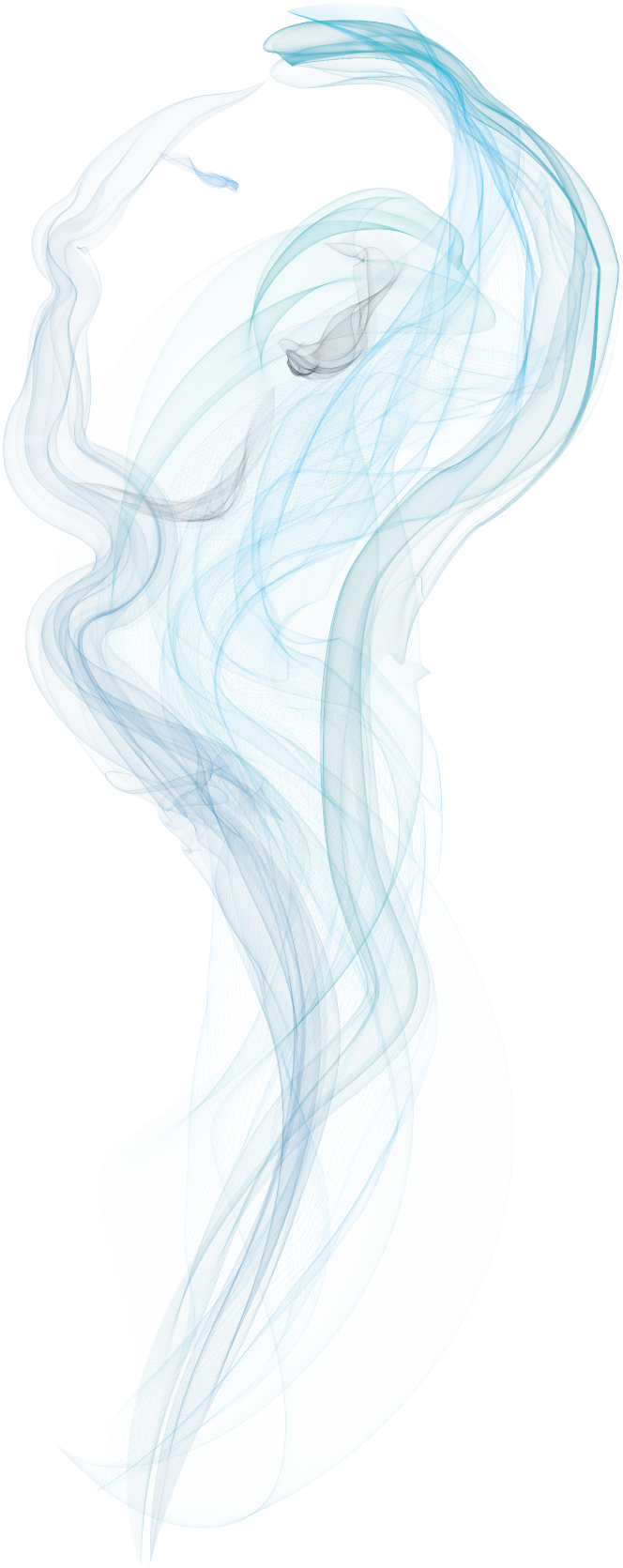

# CHAPTER 4

## Cervical dystonia: Effectiveness of a standardized physical therapy program; study design and protocol of a single blind randomized controlled trial

Joost van den Dool, PT, MSc, Bart Visser, PhD, J Hans TM Koelman MD, PhD, Raoul HH Engelbert, PT, PhD, Marina AJ Tijssen, MD, PhD

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## ABSTRACT

**Background:** Cervical dystonia is characterized by involuntary muscle contractions of the neck and abnormal head positions that affect daily life activities and social life of patients. Patients are usually treated with botulinum toxin injections into affected neck muscles to relief pain and improve control of head postures. In addition, many patients are referred for physical therapy to improve their ability to perform activities of daily living. A recent review on allied health interventions in cervical dystonia showed a lack of randomized controlled intervention studies regarding the effectiveness of physical therapy interventions.

**Methods and design:** The (cost-) effectiveness of a standardized physical therapy program compared to regular physical therapy, both as add-on treatment to botulinum toxin injections will be determined in a multi-centre, single blinded randomized controlled trial with 100 cervical dystonia patients. Primary outcomes are disability in daily functioning assessed with the disability subscale of the Toronto Western Spasmodic Torticollis Rating Scale. Secondary outcomes are pain, severity of dystonia, active range of motion of the head, quality of life, anxiety and depression. Data will be collected at baseline, after six months and one year by an independent blind assessor just prior to botulinum toxin injections. For the cost effectiveness, an additional economic evaluation will be performed with the costs per quality adjusted life-year as primary outcome parameter.

**Discussion:** Our study will provide new evidence regarding the (cost-) effectiveness of a standardized, tailored physical therapy program for patients with cervical dystonia. It is widely felt that allied health interventions, including physical therapy, may offer a valuable supplement to the current therapeutic options. A positive outcome will lead to a greater use of the standardized physical therapy program. For the Dutch situation a positive outcome implies that the standardized physical therapy program forms the basis for a national treatment guideline for cervical dystonia.

# INTRODUCTION

Cervical Dystonia (CD), or torticollis, is a disabling neurological disorder characterized by abnormal positions of the head due to involuntary muscle contractions of the neck. [1] The posture in CD patients can feature one or a combination of postures: rotation (torticollis); lateral tilting (laterocollis); flexion (anterocollis); extension (retrocollis); and lateral shift. With an estimated prevalence of 5.7 patients per 100.000 persons in Western Europe, CD is the most common form of primary adult onset dystonia which usually starts after the age of 30. [2] Pain is experienced in two-thirds to three-quarters of patients and is a major source of disability, which is strongly associated with the presence of muscle contractions and head deviations. [3-6] Decreased self-efficacy, fatigue, anxiety and depression are other factors associated with disability in cervical dystonia. [7] Research on focal dystonia's, including CD, revealed abnormalities in basal ganglia function, cerebellar function, sensory processing, motor inhibition, neuro-plasticity and somatotopic cortical organisation but the pathophysiology remains largely unclear. [8] Treatment options for CD are mainly symptomatic, aiming to reduce involuntary movements, correct abnormal head positions and reduce pain. Currently, the best evidence based treatment option is to inject the dystonic neck muscles with botulinum toxin (BTX). [9-12] The effects of BTX fluctuate over time. A peak effect occurs within 2-4 weeks after injections and is followed by a decrease of effect and return of symptoms. On average new injections are given within 12-14 weeks after the previous injections (fig 1).[13]



In addition to BTX treatment, many CD patients in the Netherlands are referred for physical therapy (PT). However, due to the rarity of CD, experience among Dutch PT's is lacking. Besides, the evidence for the effects of PT on the ability to perform activities of daily living in CD is very limited. [14] Only two small Randomized Controlled Trials (RCT) and one open controlled study investigated the effects of a PT program on CD. [15-17] All studies compared BTX treatment in combination with a PT program versus BTX treatment alone. All studies showed significant better scores on pain and disability in the groups receiving BTX treatment with an additional PT program. The PT programs in all three studies consisted of intense motor learning exercises (postural control, balance, strengthening axial musculature and facilitation of voluntary movement), and mobilization techniques of the cervical spine and dystonic muscles. PT programs varied from 40 minutes per session every other day for six weeks [16], 75 minutes per session 5 days a week for five weeks [17] up to 90 minutes a day for 2 weeks [15]. Although the results of these PT treatments were positive, it is difficult to implement them to current regular care of chronic diseases provided by physiotherapists and exercise therapists. For most patients and therapists it will not be feasible to combine such an intensive program with their daily lives and practice.

One approach towards the treatment of CD was suggested by the French physiotherapist J.P. Bleton. [18] The main goals of this program are the rehabilitation of the antagonist muscles and the control of the dystonic movements by frequent training in a functional context. Exercises are taught during one or two PT sessions a week. After teaching the patients, intensive training is

required in the patient's environment (up to 10 times a day for 10 minutes). In addition, patients are encouraged to correct the dystonic posture during their daily live activities by turning their head in the opposite direction of the dystonic posture. Eventually, patients should be able to control the dystonic movements independently. This approach with increasing control of the patients and decreasing therapist involvement seems more applicable than the intensive programs by Tassoreli, El Bahwrady and Queiroz. [15-17] The effect of the Bleton treatment has never been investigated in a large randomized controlled trial. Not only for practical reasons, but also based on the pathophysiological knowledge of CD, a longer treatment period with a more functional approach and independent continuation of the treatment program seems more appropriate for the long term benefits of PT. [15]

In the current study we developed a PT program with elements of the approach suggested by Bleton. We added current knowledge of motor (re) learning principles, coaching and principles of providing feedback in a standardized PT treatment program (table 1). This resulted in a standardized, tailored PT program comprising of a one year training that aims to improve the ability to perform daily life tasks by emphasizing independent training in the patient's own environment. [18-20] The standardized PT treatment program was developed according the AGREE standards [21] in corporation with the Royal Dutch Society for Physiotherapy (KNGF), the Society for Cesar- and Mensendieck Exercise Therapy (VvOCM) and the Amsterdam School of Health Professions (ASHP). The standardized PT program was developed within the DystonieNet, a national collaboration between neurologists and allied health professionals in research, education and treatment of CD, which was initiated by the neurology departments of four university hospitals in the Netherlands. [22] The standardized PT program aims to relearn or adopt alternative/new movement strategies to improve activities in daily life situations.

The primary objective of this study is to evaluate the effectiveness of the standardized PT program on improving the ability to perform daily life activities in CD patients compared to usual PT that is given in Dutch private practices. Both PT programs are add-on treatment to BTX-injections. Measurement will take place just prior to the BTX injections as it is hypothesized that the effects of the PT program will mainly occur in the period between the injections when the BTX wears off and symptoms return (fig 1). Secondary objectives are to evaluate the effects on severity of CD pain, quality of life, anxiety and depression.

In addition, cost effectiveness will be determined by comparing the costs and health utility of the new standardized PT program with the care as usual PT treatment. It is hypothesized that the standardized PT program will be more cost effective and more effective in improving the ability to perform daily life tasks of CD patients than regular PT.

A positive outcome of this study will lead to the development of a national treatment guideline which will be implemented via the Dutch DystonieNet.

# METHODS AND DESIGN

## Design

The study will be conducted as a multi-center single blind randomized controlled trial in three Dutch university hospitals. Patients will be randomly assigned to the experimental group or control group using a computerized randomization protocol. Patients in the experimental group will be referred to specialized PT's who are trained prior to the study to perform the standardized PT program. Patients in the control group will be referred to regular PT's and receive care as usual. All data will be collected at baseline, after six months and after one year. In order to determine the additional effects of a PT program, measurements will be performed briefly before the BTX injections at the outpatient clinics of the hospitals. This implies that we measure the effect of the PT program in a period that BTX has the least effect on the symptoms of dystonia. (fig 1.) Measurements will be performed by a blind and independent assessor since it is impossible to blind the therapists and patients for treatment allocation.



## Participants

The study aims to include 100 patients with primary CD of 30 years and older, stable on BTX treatment for more than one year. Exclusion criteria are secondary or hereditary forms of dystonia, dystonia in other body parts than the neck and patients who had surgery for the treatment of dystonia.

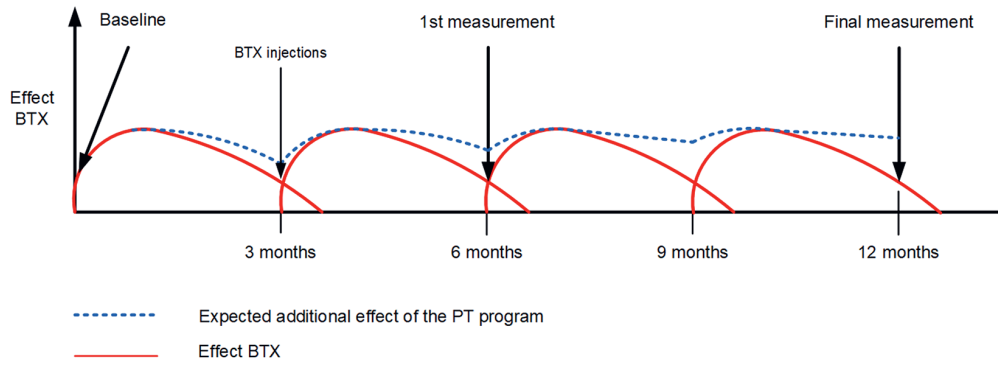


**Figure 1.** Effect of BTX and expected additional effect of PT. Effect of BTX. Increasing lines indicate a better effect of BTX and less severity of CD, pain and disability to perform daily life tasks. Red lines illustrate the normal effect of BTX, blue dotted lines illustrate the expected additional effect of the PT program.

## Interventions

### Standardized, tailored PT program

Subjects in this group receive a one year PT program according the standardized PT program in combination with BTX injections. The PT program will start two weeks after the injections. The emphasis of the PT program is on the functional performance of the exercises adapted to daily life situations, muscle stretching, passive mobilization of the neck and training principles which have found to be relevant for neural rehabilitation and motor learning and will be performed by trained physical therapists. [18-20] A summary of the theoretical basis with respect to *'muscle stretching and mobilizations'*, *'motor (re)learning'*, *'transference and generalization'*, *'feedback'* and *'self-management'*,is displayed in table 1.

### Regular PT

Subjects randomized in this group will receive BTX injections and regular PT once a week for a period of one year. In contrast to the standardized PT program, interventions are not given by specialized therapists. Due to the rarity of CD, the average therapist in the Netherlands has little knowledge about CD. It is likely that common interventions like massage, stretching and exercise of the dystonic muscles are used. Specific information of the weekly sessions and treatment will be retrieved from the local PT's after the patients finished the study period of one year.

**Tabel 1.** Principles of the standardized PT program

| **Muscle stretching /relaxation and mobilisations (de Morree [43], Fung [44])** | | |
|---|---|---|
| ***Principle*** | ***Explanation*** | ***Application in standardized PT program*** |
| 1. Passive mobilisation of the neck | Passive mobilization techniques of the neck create stress relaxation in the collagen fibers of the cervical facet joints. This helps to increase ROM. | Passive mobilisation techniques are applied by PT's |
| 2. Muscle stretching for relaxation | Stretching elongates the dystonic muscle and helps to relax it due to the Golgi tendon reflex. | Passive stretching of dystonic muscles |
| **Motor learning principles (Kleim & Jones 2008 [20])** | | |
| ***Principle*** | ***Explanation*** | ***Application in standardized PT program*** |
| 1. Use it or lose it | Failure to drive specific brain functions can lead to functional degradation. | Activation of antagonists |
| 2. Use it and improve it | Training that drives a specific brain function can lead to an enhancement of that function. | Training of antagonist in order to improve voluntary movement of the head |
| 3. Specificity | The nature of the training experience dictates the nature of the plasticity. | Functional training of activities of daily living tailored to the patients needs |
| 4. Repetition matters | Induction of plasticity requires sufficient repetition. | Exercise of newly gained tasks up to 5 times a day |
| 5. Intensity matters | Induction of plasticity requires sufficient training intensity. | |
| 6.Time matters | Different forms of plasticity occur at different times during training. | 1 year of therapy is divided in 3 stages according the 3 stages model of Fitts & Postner |
| 7. Salience matters | The training experience must be sufficiently salient to induce plasticity. | Functional training of activities of daily living tailored to the patients needs |
| 8. Age matters | Training-induced plasticity occurs more readily in younger brains. | |
| 9.Transference | Plasticity in response to one training experience can enhance the acquisition of similar behaviors. | Functional training of activities of daily living tailored to the patients needs and variation and random practice |
| 10. Interference | Plasticity in response to one experience can interfere with the acquisition of other behaviors. | |
| **Application of interventions (Shea & Morgan 1979 [45], Schmidt & Lee 2005 [46])** | | |
| ***Principle*** | ***Explanation*** | ***Application in standardized PT program*** |
| 1. Random practice | Enhances the transference and generalization of a task | Tasks or exercises are given in a random order |
| 2. Variation of practice | Enhances the transference and generalization of a task | Specific tasks or exercises are performed in different contexts |

**Table 1.** Principles of the standardized PT program (*continued*)

| **Feedback (Shea et al. 1993 [47], Schmidt & Lee 2005 [46])** | | |
|---|---|---|
| ***Principle*** | ***Explanation*** | ***Application in standardized PT program*** |
| 1. Summary Knowledge of Results | Feedback is essential for learning to take place. Summary KR is that KR is given after an entire set of trials during an exercise instead of after each individual trial. It is the most effective form for the retention and transference of a task. | Feedback is given after each set of trials of a task. Each task is performed at least 5 times after feedback is provided |
| **Self-management (Fitts & Posner three-stage model [48])** | | |
| ***Principle*** | ***Explanation*** | ***Application in standardized PT program*** |
| 1. Cognitive phase | The learner is concerned with understanding a task and developing strategies to perform a task and how the task can be evaluated. These efforts require a high degree of cognitive activity | During the first month patients receive 2 PT sessions a week to (re)learn and understand movement strategies. Movement strategies will be practiced at home 5–10 times a day for 10–15 minutes |
| 2. Associative phase | The learner has selected the best strategy for a task and starts to refine it. This stage requires less cognitive activity | During this stage patients receive 1 PT session. Movement strategies from the first stage will be increased in difficulty. Movement strategies will be practiced at home 5–10 times day for 10–15 minutes |
| 3. Autonomous phase | The learner is able to perform a skill automatically. A low degree of attention is required. | During the last (autonomous) stage, patients are encouraged to perform the learned tasks independently and to improve and maintain their (re)gained abilities themselves. Therapists will have a coaching role. Patients receive one PT session a month for additional advice and motivation. |

## Outcome variables

### Disability

Disability as measured with the disability subscale of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) is the primary outcome of this study. The TWSTRS scale is a widely used scale in research and is a valid and reliable tool to measure severity, disability and pain in CD (Kendall Tau = 0.85, $p < 0.01$). [23,24] The disability section is a six point Likert scale which consists of six items like driving a car, reading and performing ADL activities (max 30 points). Lower scores indicate less disability.

Disability will also be measured with the Functional Disability Questionnaire (FDQ). The FDQ is a 27 item scale to measures the impact of CD on daily functioning. Questions are asked about the extent to which CD affects the engagement in and performance of a sample of activities at the present time. Each item is rated on a 5-point scale (maximal score 68 points) The FDQ has a high reliability ($r=.93$, $P<0.001$). [25]

**Severity of CD**

Severity of CD will be measured with the Tsui scale. [26] The Tsui scale measures different aspects of abnormal posture and movements in CD patients. It has a maximal score of 25 points. The Tsui-scale is a widely used, standardized and reliable scale (ICC=.86) to measure the severity of CD. [26] Lower scores indicate less severity of dystonia.

Severity of CD will also be measured with the Clinical Global Impressions-Severity of

Illness Scale (CGI-S) and the Clinical Global Impression - Improvement scale (CGI-I). Both scales are observer- or patient- rated scale that measure illness severity and global improvement on a 7-point scale. Both scales are widely used and reliable and validated for a numerous of disorders (r=0.41 to 0.77, p=0,05 for self-perceived measures and r=0.36 to 0.84, p=0.05 of clinician administered measures of anxiety, depression, impairment and quality of life). [27,28]

**Active Range of Motion**

To determine the changes in the ability to perform voluntary movements, active range of motion (AROM) will be measured with a cervical range of motion meter (CROM). [29] The CROM is a frame that will be placed on the head with three separate inclinometers to measure AROM in the sagittal, coronal and horizontal planes. First the resting position of the head will be measured and subsequently the AROM of flexion, extension, lateral flexion and rotation. Although the psychometric properties of the CROM in patients with CD are unknown, in a healthy population the CROM is a reliable instrument to measure cervical ROM (intratester reliability ranged .63-.93 intertester reliability ranged .74 -.87). [29] To determine the additional effects of PT on pain, patient are asked to rate their pain on a Numeric Rating Scale (NRS). A score of 0 means no pain and a score of 10 means the worst pain imaginable. The NRS is a validated and reliable tool for the assessment of pain (Spearman r =.94 between VAS and NRS, test-retest reliability ICC = .90). [30,31]

**Quality of Life**

Quality of Life (QoL) will be measured with the Cranio-cervical Dystonia Questionnaire (CDQ-24) and Short Form 36 (SF-36). [32,33] The CDQ-24 is a validated and disease specific, self-reporting questionnaire to evaluate quality of life of patients with cervical dystonia on a five point likert scale. [32] The CDQ-24 subscales showed moderate to high correlations with those SF-36 subscales measuring similar aspects (Pearson's correlation r = 0.50–0.73; p,0.001, each).The score ranges from 0 to 96 points where lower scores indicate a better QoL. The SF-36 is a validated generic measure for QoL containing 36 items measuring eight dimensions of health. [33] Scores of the different dimensions can range from 0 (worst) to 100 (best).

**Anxiety and Depression**

Since 25 to 59% of the CD patients suffer from anxiety disorders or depression [25,34], the effects of PT are determined with the Beck's Anxiety Index [35] and Beck's Depression Index. [36,37] Both instruments

are validated and reliable tools and are rated on a 21 item 4 point Likert scale (BDI: r=.73 with Hamilton Psychiatric Rating Scale for Depression. BAI: test-retest reliability coefficient of .67, R=.54, p=0.05 with anxiety).

**Cost effectiveness**

To determine the cost effectiveness of both physical therapy programs, the costs per quality adjusted life year (QALY) will be calculated. In addition, cost-effectiveness related to the clinical outcome will be calculated, with the costs per unit on the TWSTRS-disability scale as the outcome measure. Costs which are associated with loss of productivity due to disability or inability to work will be registered in the subgroup of patients below the age of 65 with the Productivity Costs Questionnaire (PCQ) and EuroQoL-5D (EQ-5D). The PCQ is a 22 item generic questionnaire used to measure absence of work due to health problems and is advised as standard instrument for use in economic evaluations of Dutch healthcare. [38,39] The EQ-5D is a six item, standardized measure of health status in order to provide a simple, generic measure of health for clinical and economic appraisal. [39,40]

## Sample size

The power calculation is based on the study by Brans et al. investigating the long term effect of BTX on disability and functional health. [41] This study showed an average improvement of 7.1 out of 30 points on the disability subscale of the TWSTRS after 1 year of BTX treatment in CD patients. It is estimated that the additional effect of the PT program according the treatment guideline will be at least half the effect caused by BTX. The cut off for the success of the PT program is therefore, set on an average improvement of 3.5 out of 30 points on the TWSTRS disability scale which is clinically relevant according Brans et al.[42]. With a power of 0.80 and an alpha of 0.05, each group will need 44 subjects. With a loss of 10% taken into account, 50 subjects in each group are required.

## Analysis

Differences in all outcome measures, with exception of the measures for cost effectiveness, will be determined with a mixed between-within (repeated measures) analysis of variance for both treatment arms, across three time periods (baseline, after six months and one year). All analyses will be performed under the intention to treat principle in SPSS 20.0. Differences will be considered significant at p-value < 0.05.

The cost effectiveness will be determined by a cost-utility analysis from a societal perspective with a time horizon of one year. Cost-utility analysis facilitates the comparative assessment of health care innovations across different types of interventions, disease areas and health care settings. Incremental cost-utility and cost-effectiveness ratios for the add-on standardized PT program versus add-on regular PT will be calculated as the extra costs per QALY gained and the extra costs per unit decrease in TWSTRS-disability score. The cost effectiveness will be calculated according

the most recent guidelines for unit costing in healthcare research. [40] The friction cost method will be applied to calculate the costs of production loss as measured with the PCQ, EQ-5D. Unit costs of production loss will be based on the most recent national guidelines for unit costing in healthcare research. [40] The base year for unit costing will be 2013.

### Ethical considerations

In accordance with the local medical ethics committee (MEC) guidelines, written informed consent is required from participants who fulfil the selection criteria. The study has been approved by the Medical Ethics Committee of the Academic Medical Center, Amsterdam (MEC 2012_048). This study is registered under Trial registration number NTR3437 of the Dutch trial registration (Nederlands Trial Register).

## DISCUSSION



In our study we aim to fill the gap in evidence based medicine to treat CD patients with PT by performing a large RCT towards the (cost) effectiveness of a standardized, tailored PT program. There are several differences of this study compared to studies reported in the current available literature.

Although other studies have showed added value of short, high intensity PT program on pain and disability in combination with BTX treatment, follow-up measurements were not performed and therefore it is not known if a wash out of treatment effects will occur. [15-17] Since CD is a life lasting disorder, a longer treatment period seems more appropriate to establish lasting changes. We therefore choose for a treatment period of one year in contrary to the other studies which lasted five weeks maximal. [15-17] Another difference with other studies is that the standardized PT program tends to teach patients themselves, how to improve their ability to perform daily life tasks and to manage their symptoms in their own environment. To establish lasting changes and the ability of patients to manage their symptoms in their own environment, we have chosen for a treatment period of one year. The standardized treatment program itself is based on modern principles about motor learning, transference and generalization of learned tasks to enhance lasting (neuroplastic) changes (table 2.). [20,43-47] Based on these principles, we aimed for a tailored, evidence based intervention that is thought to be more effective than regular interventions.

It is hypothesized that the overall added effect of the standardized PT program on the BTX treatment lies between the periods that the BTX is starting to wear off and the BTX is starting to work again after new injections (Fig 1.). Other studies performed measurements in the periods when the peak effect of BTX occurred (2-4 weeks after injections) which make it impossible to determine the additional effects of a PT program on CD. [15-17] We therefore choose to measure the effects of PT just prior to the BTX injections when the interference of BTX effects are minimal.

Another goal of the standardized treatment program is to make patients less dependent of healthcare providers and to decrease the healthcare costs for this patient group.

In the Netherlands many CD patients are referred for physical therapy. Since CD is a chronic indication for PT, patients receive (except for the first 20 treatments) unlimited reimbursement for PT which results in long lasting use of healthcare in the current, regular situation. We therefore added an economic evaluation to compare the cost effectiveness of the standardized PT program with physical therapy care as usual.

### Future implications

In the case of a positive outcome of this study, the standardized PT program will be used as a basis for a national treatment guideline which will be implemented via the Dutch DystonieNet.

## COMPETING INTERESTS

J.H.T.M. Koelman and M.A.J. Tijssen received an unrestricted research grant from Ipsen Pharmaceutical and Allergan Inc. for studies and teaching workshops on dystonia and from Ipsen to finance a specialized dystonia nurse. Ipsen and Allergan have no role in study design, collection, analysis, interpretation of data, in the writing of the report and in the decision to submit the paper for publication. The other authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

JD wrote the first draft of the manuscript and BV, RE, HK and MKT contributed to the completion of the manuscript. All have made substantial contributions to conception and design of the study.

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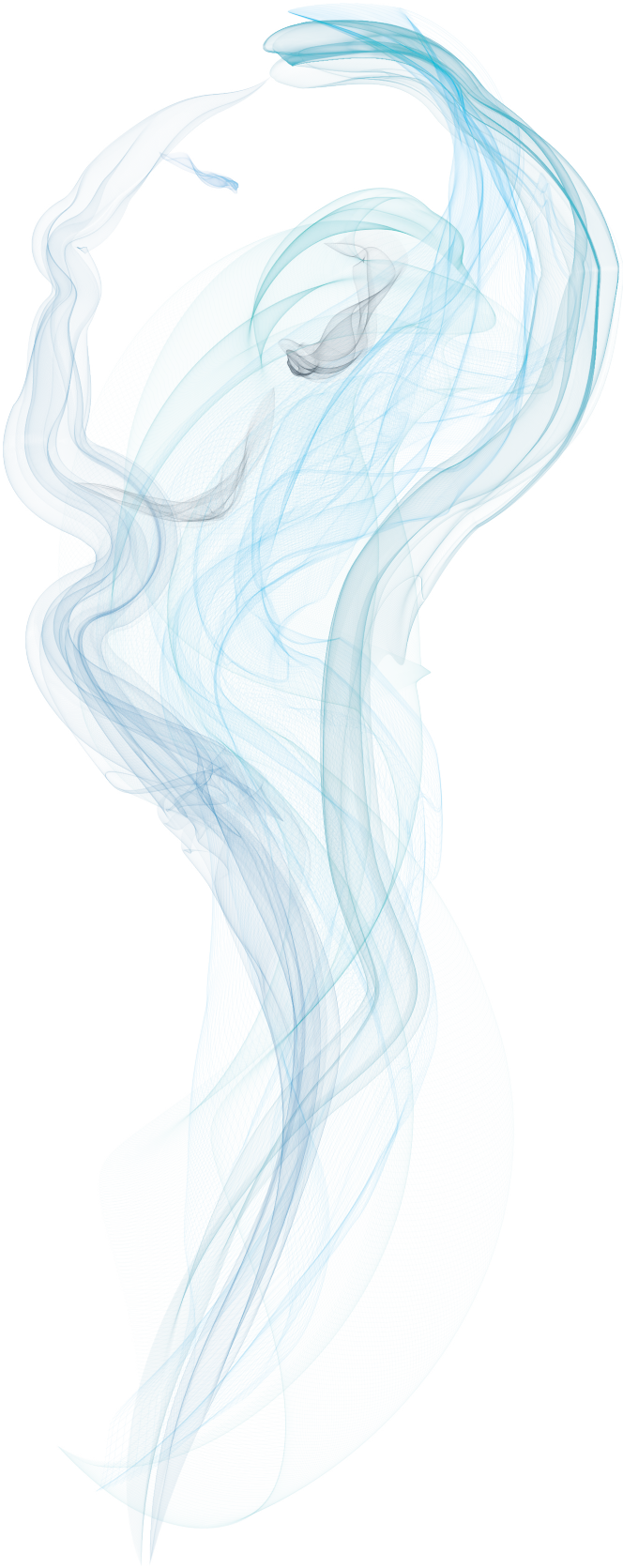

# CHAPTER 5

## Long-term specialized physical therapy in cervical dystonia: outcomes of a randomized controlled trial

Joost van den Dool, PT, MSc, Bart Visser, PhD, Johannes H.T.M. Koelman, MD, PhD, Raoul H.H. Engelbert, PT, PhD, Marina A.J. Tijssen, MD, PhD

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## ABSTRACT

**Objective:** To evaluate the effectiveness of a specialized physical therapy (SPT) program on disability in cervical dystonia (CD) compared to regular physical therapy (RPT).
**Design:** A single blinded randomized controlled trial.
**Setting:** This study was performed by physical therapist in a primary healthcare setting. Measurements were performed at baseline, six and 12 months in the Botulinum Toxin (BoNT) outpatient clinic of the neurology department.
**Participants:** 96 patients with primary CD and stable on BoNT treatment for one year.
**Main outcome measures:** The primary outcome was disability assessed with the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Secondary outcomes were, pain, anxiety, depression, quality of life and health related costs over 12 months.
**Results:** 72 participants (30 males/ 42 females) finished the study: 40 received SPT, 32 RPT. No significant between group differences were found after 12 months of treatment (p=.326). Over these 12 months both groups improved significantly (p<.000) on the TWSTRS disability scale compared to baseline (SPT 1.7 points, RPT 1.0 points). SF-36 General Health perceptions (p=.046) and self-perceived improvement (p=.007) showed significantly larger improvements after 12 months in favour of SPT. Total health related costs after 12 months were $1,373 (SD 556) for SPT compared to $1,614 (SD 917) for RPT.
**Conclusion:** SPT revealed no significant differences compared to RPT after 12 months of treatment on the TWSTR disability scale. Both groups showed similar improvements compared to baseline. Positive results in the SPT group were higher patient perceived effects and general health perception. Treatment costs were lower in the SPT group. With lower costs and similar effects, the SPT program seems to be the preferred program to treat CD.

# INTRODUCTION

Cervical dystonia (CD) is a neurological movement disorder characterized by involuntary muscle contractions causing abnormal postures and/or twisting movements of the head and neck.[1] With a prevalence of 4.9 (95% CI 3.6 to 6.9) per 100,000 persons, it is the most common form of dystonia.[2] Patients may also experience non-motor symptoms including pain, anxiety, depression, and loss of self-confidence.[3] Pain is reported by 75% of the patients causing limitations in daily life activities (ADL).[4] The main treatment option is botulinum toxin (BoNT) injections in affected muscles to improve head postures and reduce pain.[5] However, BoNT treatment is often unsatisfactory: many patients maintain difficulties performing daily tasks. In addition to BoNT treatment, patients are often referred for physical therapy (PT), but there is little evidence regarding the long-term effectiveness.

The effect of PT in CD has been studied in three, small randomized controlled trials (RCT) and one open controlled study.[6–10] These studies compared BoNT treatment alone with a combined PT and BoNT treatment. PT consisted of short, intensive programs with various PT modalities, varying from 40 minutes per session every other day for six weeks, up to 90 minutes a day for two weeks.[8,10] Despite significant improvements on pain and disability, as measured with TWSTRS, their high intensity and frequency make these programs difficult to implement in daily practice.



An internationally accepted and less intensive PT intervention was described by Bleton.[11] It aims to strengthen the (non-dystonic) antagonist muscles by repetitive exercises and to learn/re-learn motor skills. Two studies have compared the Bleton method to other PT treatments.[9,12] Both studies showed overall improvements without significant differences between treatments on all domains of the TWSTRS after a 12- and 24-week PT program. Limitations of these studies were a small population with and without BoNT treatment in the study of Boyce et al. [9] and treatment given by the same therapists in both the experimental and control group in the study of Counsell et al.[12]

Besides the limitations of these studies, current PT treatment is based on the experience of individual therapists with no standardization. Since CD is relatively rare, experience among therapists is often lacking. To overcome the limitations in the available studies and to improve PT treatment for CD patients, a specialized PT program was developed in 2012 as part of the Dutch DystoniaNet initiative (www.dystonia.net).[13] This PT program combines the Bleton method with motor learning/re-learning principles, coaching, and principles of providing feedback in a structured way. [13,14] To determine if it is worthwhile to train PT's according to the SPT program, we aimed to evaluate the effects of SPT compared to RPT in addition to BoNT treatment, on disability in CD patients (after six and 12 months) and on healthcare costs.

# METHODS

## Study design

The study was performed as a multi-center, single blinded, randomized controlled trial and approved by the Medical Ethics Committee of the Academic Medical Centre, Amsterdam.

## Participants

From November 2012 to June 2015, participants were recruited from the neurology departments of 16 hospitals, using the following inclusion criteria: primary CD, 30 years or older, stable on BoNT treatment for over a year. Participants with secondary or hereditary forms of dystonia, dystonia in other body parts than the neck, other neck conditions, treated with deep brain stimulation or selective nerve denervation were excluded. Written informed consent was obtained from all participants.

## Masking and randomization

After baseline measurements, participants were allocated to SPT or RPT using a computerized block randomization protocol (with a maximum block size of 4). An independent research assistant sent the randomized group allotment to participants in sealed envelopes by mail. Based on the random allotment, participants either contacted a regular or a trained PT in their residential area to start treatment within two weeks after their BoNT injections. Envelopes for the SPT group included a list of trained therapists sorted by residential area.

## Procedures

### Data collection

To determine the effects of PT, data was collected just prior to the next BoNT injections when interference of BoNT effects was minimal.[13] Data on the severity of dystonia was collected at baseline, 6 and 12 months by one blinded, independent assessor. Other data was collected through self-reported questionnaires. Participants were instructed not to discuss the nature of the PT they received with the assessor. Participants in the control group were offered SPT after finishing the study.

### Specialized PT program

The experimental group received 12 months of SPT [13] consisting of exercises with emphasis on motor training to correct the dystonic postures during ADL, according to principles relevant for neurological rehabilitation and motor learning.[14] Stretching of dystonic muscles was used for temporary relaxation (inhibition) and to decrease possible contractures due to continuous contractions. Passive mobilizations were used to increase range of motion and to decrease possible arthrogenic limitations as a consequence of continuous abnormal postures. [14] During the first six weeks participants received two PT sessions of 30 minutes a week. After six weeks participants

received one session a week for up to six months. Subsequently patients received one PT session a month focused on coaching the patient and independent continuation of the training. Daily home-based exercises had to be performed up to 5 times a day for 10-15 minutes per session over the entire treatment period.[14] Training of the PT's consisted of a one-day course, including background information on dystonia in general and on CD specifically. A detailed description of the program is added in the supplementary material.

**Regular PT**

The control group received RPT once a week for 12 months. In contrast to the SPT program, interventions were given by regular PT's with no extra training on dystonia, and were qualified as 'care as usual'. RPT interventions included massage, relaxation exercises, stretching, and general exercises of the neck. No format was provided regarding the intensity and frequency of the sessions.

## Outcome measures

The primary outcome was disability as measured with the disability subscale of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).[16,17] Disability was also measured with the Functional Disability Questionnaire (FDQ) as a secondary disability outcome.[15]



Other secondary outcomes included pain, motor severity of dystonia, anxiety, depression, self-perceived improvement, quality of life (QoL) and health related costs of PT after 12 months. Pain was measured by the TWSTRS pain subscale and a Numeric Rating Scale (NRS).[16–18] Motor severity with the TWSTRS severity subscale and Tsui scale.[16,17,19]Anxiety and depression levels were determined with Beck's Anxiety Inventory (BAI) and Beck's Depression Inventory (BDI).[20,21]

Self-perceived improvement was assessed with the Clinical Global Impression - Improvement scale (CGI-I), a patient-rated instrument that measures global improvement on a 7-point scale.[22]

QoL was assessed with Short Form 36 (SF-36) and the Craniocervical Dystonia Questionnaire (CDQ-24), a disease specific instrument to evaluate the QoL of CD patients.[23,24] A detailed description of the used outcome measures can be found in the published protocol of this study.[13]

Total societal costs were determined by the sum of treatment costs, travel costs and costs due to productivity loss (based on the friction cost method).[25] Costs were calculated in dollars for each treatment arm according the standardized cost prices for unit costing in health care research.[26] Subsequently, differences in total societal costs between the two treatment arms were calculated.

## Statistical analyses

### Sample size

Power calculation was based on the study by Brans et al.[27] investigating long-term effects of BoNT on disability in CD; they showed a mean improvement of 7.1 points on the TWSTRS disability subscale after 1 year. We considered the additional effect of SPT should be at least 50% (i.e. 3.5 points on the TWSTRS disability scale) of the effect due to BoNT. With a power of 0.80 and an alpha of 0.05, each group needed 44 subjects. Taking into account a loss of 10%, 50 subjects per group were required.

First, descriptive statistics (frequencies, means, standard deviations (SD)) for patient characteristics and adherence were calculated for each group. A Kolmogorov-Smirnov test was used to assess whether there was a normal distribution of the variables. Despite randomization there was a significant baseline difference on the FDQ (Mann-Whitney U p= 0.003): participants in the SPT group scored worse with higher levels of disability. Differences on the other outcomes were not significant but nonetheless substantial. To correct for these and to determine the changes of the groups relative to each other, data were centered at baseline. Subsequently, missing data from dropouts at 12 months were imputed using an expectation maximization algorithm. A mixed between-within subjects ANOVA was used to test for changes over time and group differences. In case of significant main or interaction effects post hoc tests were performed. Finally, a Fisher's exact test was used to determine differences after 12 months for self-perceived improvement. P-values <0.05 were considered statistically significant. Descriptive statistics (means, standard deviation, confidence intervals) were used to determine the health related costs for both treatment arms. Analyses were by intention-to-treat and performed in Statistical Package for Social Sciences version 22.0.

# RESULTS

A total of 96 participants (59 females, 37 males) with a mean age of 58.4 years (SD 9.2, range 38-79) and a mean disease duration of 12.7 years (SD 10.4, range 1-52 years) were randomly allotted to SPT or RPT between November 2012 and June 2015 (Table 1).

Of the 96 participants, 24 withdrew and did not complete the assessment at 12 months. Three participants withdrew immediately after randomization and 21 (8 experimental, 13 controls) discontinued participation due to co-morbidity unrelated to the study or inability to attend PT sessions (figure 1). A total of 72 participants finished the study: 40 received SPT, 32 RPT. Participants in the SPT group attended 31 PT sessions on mean (SD 11). Participants receiving RPT attended 41 sessions on mean (SD 24).

**Table 1.** Patient baseline characteristics

| | Specialized PT (n=48) | Regular PT (n=48) |
|---|---|---|
| Gender male (%) – female (%) | 19 (38.5%)-29 (61.5%) | 18 (37.5%)-30 (62.5%) |
| Age mean (SD), range in years | 59.3 (9.3), 37-79 | 57.1 (9.3), 42-75 |
| Disease duration mean (SD), range in years | 13.7 (10.8), 1-52 | 11.5 (10.2), 1-52 |
| Presence of dystonic head tremor<br>With tremor (%) – Without tremor (%) | 23 (47.9%) – 25 (52.1%) | 15 (31.3%) –33 (68.8%) |
| Main direction dystonia | Torticollis: 28 (58.3 %)<br>Laterocollis: 14 (29.2%)<br>Retrocollis: 2 (4.2%)<br>Anterocollis: 4 (8.3%) | Torticollis: 25 (52.1 %)<br>Laterocollis: 18 (37.2%)<br>Retrocollis: 1(2.1%)<br>Anterocollis: 4 (8.3%) |
| TWSTRS Disability scale (SD) | 7.83 (4.60) | 6.39 (3.39) |
| Functional Disability Questionnaire (SD) | 42.02 (13.11) | 35.20 (13.51) |
| TWSTRS pain scale (SD) | 7.49 (6.04) | 6.39 (5.24) |
| NRS pain scale (SD) | 3.50 (3.16) | 3.16 (3.15) |
| TWSTRS severity scale (SD) | 16.91 (4.88) | 16.00 (5.10) |
| Tsui severity scale (SD) | 9.81 (3.41) | 8.66 (3.13) |
| Beck Depression Index (SD) | 8.9 (6.63) | 7.66 (6.94) |
| Beck Anxiety Index (SD) | 30.81 (7.84) | 29.14 (7.89) |
| SF-36 (SD) | | |
| -Physical Functioning | 75.72 (18.56) | 79.68 (16.54) |
| -Role limitations Physical Functioning | 51.56 (44.48) | 56.10 (37.80) |
| -Bodily Pain | 56.68 (21.18) | 63.91 (21.38) |
| -Social Functioning | 75·57 (21.18) | 77.60 (25.25) |
| -Mental Health | 71.58 (17.48) | 74.91 (19.67) |
| -Role limitations Emotional problems | 79.86 (34.88) | 77.08 (35.83) |
| -Vitality | 57.18 (21.58) | 64.79 (19.32) |
| -General Health perceptions | 56.35 (19.77) | 63.20 (21.00) |
| CDQ-24 (SD) | | |
| -Stigma | 31.51 (23.61) | 27.43 (20.82) |
| -Emotion | 24.16 (21.04) | 17.18 (16.91) |
| -Pain | 31.77 (24.83) | 23.61 (26.03) |
| -Activities of Daily Living | 31.33 (21.67) | 24.30 (18.01) |
| -Social | 12.36 (17.46) | 7.55 (12.76) |

Note: Lower scores indicate less severe symptoms for all outcome measures except for the SF-36. Higher SF-36 scores indicate fewer symptoms

Legend: TWSTRS=Toronto Western Spasmodic Torticollis Rating Scale, NRS=Numeric Rating Scale, CDQ-24=Cranio-cervical Dystonia Questionnaire

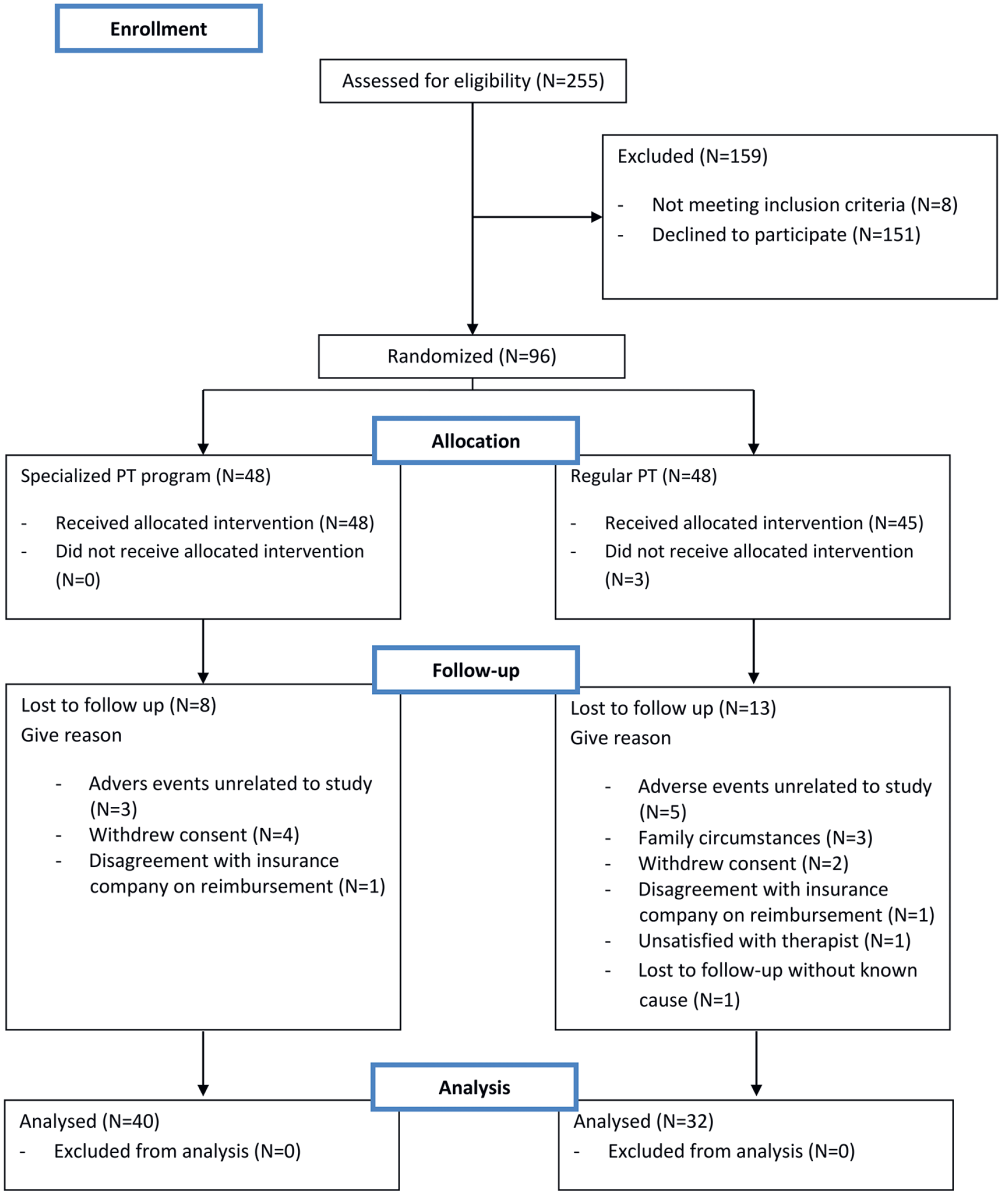


**Figure 1.** Flow chart of patient enrollment

On the primary outcome disability, no significant between group differences were found after 12 months of treatment (p=.326) on the TWSTRS disability scale. For the secondary outcomes, only two showed significant differences between the groups: General Health perceptions measured with the SF-36 (P=.046) and self-perceived improvement by patients (P=.007). Differences between groups and mean changes per group after 12 months are shown in figures 2a and 2b.

Ten out of the 22 outcomes showed improvement over time in both groups, with most of the improvement occurring in the first six months. On the primary outcome disability, both groups improved significantly compared to baseline on the TWSTRS disability scale (SPT 1.7 points, RPT 1.0 points, p=.000). The FDQ showed no significant between group differences nor improvement over time. Main effects over time from the ANOVA and post-hoc analysis to see how changes occurred over time are shown in table 2.

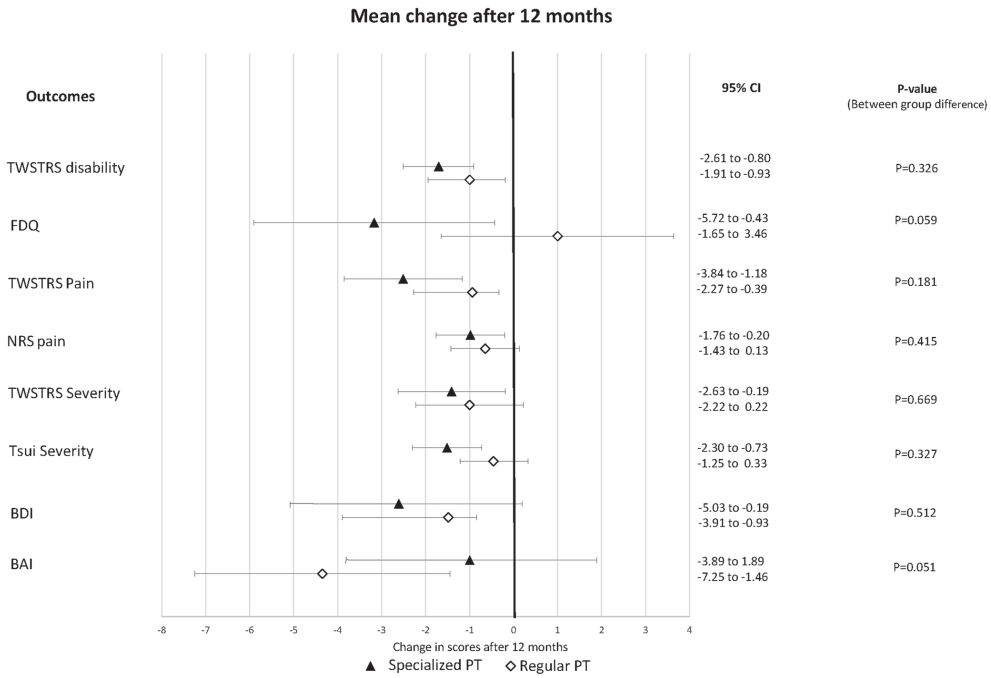


**Figure 2a.** Mean changes after 12 months on disability, pain, severity, depression and anxiety. Note: Negative values represent improvement.
Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; NRS, numeric rating scale.

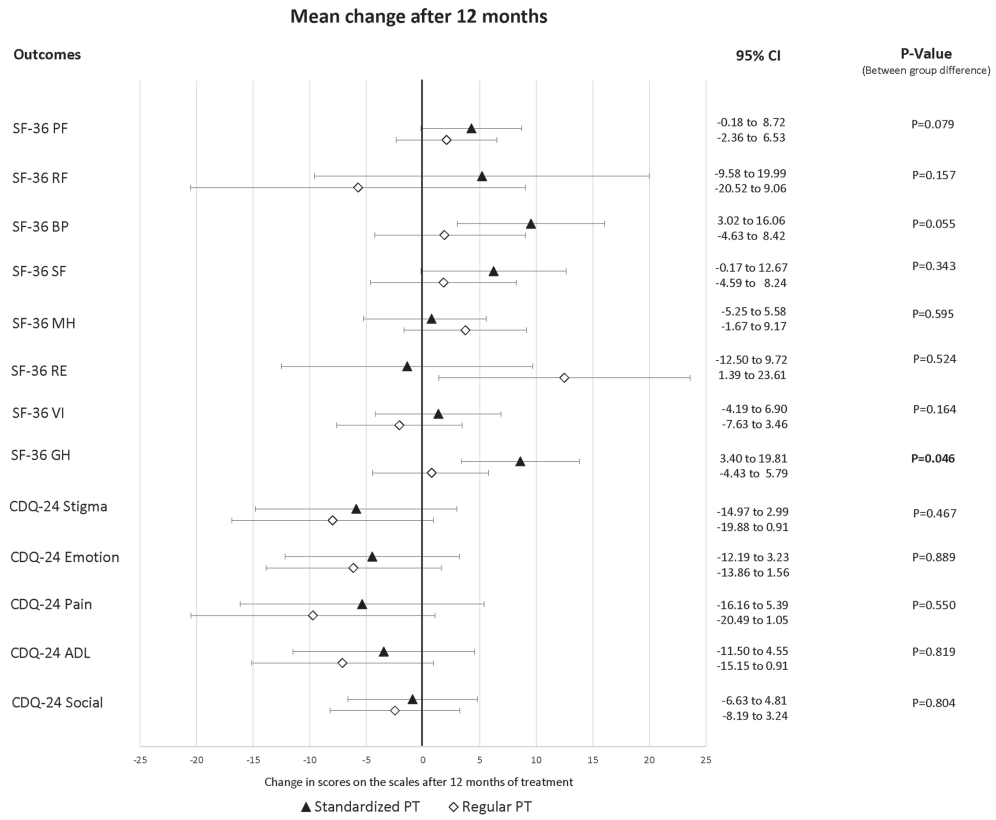


**Figure 2b.** Mean changes after 12 months on quality of life measured by the SF-36 and CDQ-24. Note: Positive values on the SF-36 represent improvement, negative values on the CDQ-24 represent improvement.
Abbreviations: BP, Bodily Pain; GH, General Health Perceptions; MH, Mental Health; PF, Physical Functioning; RE, Role Limitations Emotional Problems; RP, Role Limitations Physical Functioning; SF, Social Functioning; VI, Vitality.

**Table 2.** Main effect of time

| Outcome | Wilk's lambda | F (df) | P-value | Effect Size | Post-HOC* |
|---|---|---|---|---|---|
| TWSTRS Disability scale | .84 | 9.20 (2,93) | .00 | .17 | T0>T1; T0>T2 |
| Functional Disability Questionnaire | .98 | .80 (2,93) | .45 | .02 | N/A |
| TWSTRS pain scale | .86 | 7.32 (2,93) | .00 | .14 | T0>T1; T0>T2 |
| NRS pain scale | .89 | 5.31 (2,93) | .01 | .10 | T0>T1; T0>T2 |
| TWSTRS severity scale | .92 | 3.83 (2,93) | .03 | .08 | T0>T1; T0>T2 |
| Tsui severity scale | .81 | 10.67 (2,93) | .00 | .19 | T0>T1; T0>T2 |
| Beck Depression Index | .88 | 6.10 (2,93) | .03 | .11 | T0>T1 |
| Beck Anxiety Index | .93 | 3.37 (2,93) | .04 | .07 | T0>T2 |
| SF-36 | | | | | |
| -Physical Functioning | .96 | 2.10 (2,93) | .12 | .05 | N/A |
| -Role limitations Physical Functioning | 1.00 | .00 (2,93) | .99 | .00 | N/A |
| -Bodily Pain | .93 | 3.30 (2,93) | .04 | .07 | T0>T2 |
| -Social Functioning | .94 | 3.08 (2,93) | .05 | .06 | N/A |
| -Mental Health | .97 | 1.45 (2,93) | .24 | .03 | N/A |
| -Role limitations Emotional problems | .97 | 1.67 (2,93) | .19 | .04 | N/A |
| -Vitality | .99 | .07 (2,93) | .93 | .00 | N/A |
| -General Health perceptions | .92 | 4.12 (2,93) | .02 | .08 | T0>T2 |
| CDQ-24 | | | | | |
| -Stigma | .95 | 2.52 (2,93) | .09 | .05 | N/A |
| -Emotion | .95 | 2.43 (2,93) | .09 | .05 | N/A |
| -Pain | .94 | 2.97 (2,93) | .06 | .06 | N/A |
| -ADL | .97 | 1.71 (2,93) | .19 | .04 | N/A |
| -Social | .98 | 1.09 (2,93) | .34 | .02 | N/A |

Legend: TWSTRS=Toronto Western Spasmodic Torticollis Rating Scale, NRS=Numeric Rating Scale, CDQ-24=Cranio-cervical Dystonia Questionnaire, ADL=Activities of Daily Living
* Post-Hoc Analysis with Bonferroni correction when main effect of time P < .05. T0=baseline, T1=six months, T2=12 months, N/A=Not Applicable

Secondary outcomes pain, severity of dystonia, anxiety and depression all showed significant improvements (Table 2)over time for both groups (TWSTRS pain p=.000, NRS p=.007, TWSTRS severity p=.025, Tsui p=.000, BAI p=.039, BDI=.003). On QoL a significant change over time was also found for both groups (table 2) on the SF-36 General Health perceptions (p=.019) and Bodily Pain domain (p=.041). The other domains showed no differences at all. None of the domains of the CDQ-24 showed significant between group differences or changes over time.

Self-perceived improvement showed a significant difference in favor of SPT after 12 months (p=.007). In the SPT group, 30 participants (78,9%) reported improvement of their symptoms; 8 (21.1%) reported no improvements, and none reported worse symptoms. In the RPT group, 16 participants (51.6%) reported improvement of their symptoms while 10 (32.2%) reported no improvements, and 5 (16.2%) reported worse symptoms.

Total societal costs for SPT were 1,373 (SD 557) and for RPT 1,614 (SD 917) dollar on average (table 3). This difference was mainly caused by lower treatment costs for SPT with a mean difference of 366 dollar per patient (95% CI -650 to -82). Travel costs and costs for productivity loss were 98, (95% CI 47 to 148) and 28 dollar (95% CI -50 to 106) higher in in the SPT group, making the total mean costs for SPT 240 dollars (95% CI -550 to 69) lower compared to RPT.

**Table 3.** Cost components and total costs in dollars

| | SPT Mean (SD) | RPT Mean (SD) | Mean difference (95% CI) |
|---|---|---|---|
| **Nr. of PT sessions** | 31 (11) | 41 (24) | -9.6 (-17.1 to -2.2) |
| **Treatment costs** | 1175 (421) | 1541(888) | -366 (-650 to -82) |
| **Travel costs** | 137 (173) | 39 (23) | 98 (47 to 148) |
| **Costs productivity loss** | 61(216) | 33(164) | 28 (-50 to 106) |
| **Total costs** | 1373(557) | 1614 (917) | -240 (-550 to 69) |

Note: Prices in dollars are based on the exchange rate of October 19th 2018 where 1 euro represents 1.145 dollar.

## DISCUSSION

This is the first RCT studying the long-term effectiveness of SPT in patients who were stable on BoNT treatment. Both SPT and RPT improved on the TWSTRS Disability scale over time. However, no significant differences between groups were found although a small trend towards better outcomes was seen for SPT on most outcomes. The SPT group improved significantly on self-perceived improvement and General Health perceptions. Furthermore, healthcare costs in the SPT group were 240 dollar lower per patient on average.

These findings are in line with two recent studies comparing the Bleton method with other PT interventions describing an overall positive effect of PT without significant differences between groups.[9,12] A possible reason for small group differences is that a one day training course for SPT therapists is not sufficient to discriminate enough between the two treatment arms. Longer training could provide the necessary experience for SPT to be more distinctive. Besides, Dutch PT's are well educated and trained to find best evidence/best practice interventions. Interventions used in the RPT group also included exercises aimed at correcting dystonic postures like the Bleton method, possibly creating an overlap between the two treatments causing to little contrast. However, it is expected that over time SPT therapists become more experienced. By being part of the DystoniaNet, SPT therapists will treat more CD patients improving their treatment skills.

Average costs were lower for the SPT group than for the RPT group. These lower costs are largely due to lower treatment costs reflecting the smaller amount of treatment sessions needed for SPT. As expected, travel costs for SPT were higher because the number of SPT therapists in a certain

area was lower than the number of RPT therapists, implying a larger distance to the nearest SPT therapist. With the training of more therapists in the near future, distances and therefore travel costs will decrease. An additional reduction in costs might be achieved when SPT/RPT contribute to diminished BoNT use, either by reducing the necessary dose or extending the period between injections. [8] It is worthwhile to include costs for BTX treatment in future studies.

In recent years, the importance of psychological factors in dystonia has been recognized.[3] In our study both groups showed moderate percentages of anxiety and depression at baseline with significant improvements in both groups over time. This is important as psychological factors are major contributors to disability in CD, which was recently confirmed in the current study's cohort. [28] PT can improve psychological factors because it aims at improving the ability and self-confidence to function independently in daily life.

Although our primary focus was on the between-group effects, the positive effects seen for most outcome measures for both groups are worth mentioning (table 2). Participants in our study had received BoNT treatment for more than one year with stable effects, and then combined it with SPT or RPT. Increasing benefits due to BoNT during the study period were not expected because BoNT is well known to have long-lasting and stable beneficial effects in most CD patients.[29] Benefits measured in this study may therefore be the result of either SPT or RPT, and are in line with a report on a six-week PT program in addition to BoNT treatment compared with BoNT treatment alone.[8] There is always a possibility however, that some of the positive effects may be caused by participating in a study with a special interest in dystonia (Hawthorne effect).



Dystonia patients have altered neuro-plasticity and somatotopic cortical organization compared to controls.[30] Improvements by PT might be related to changes in maladaptive neuroplasticity of the sensory-motor cortices, as the SPT program was based on motor learning principles known to enhance neuroplastic changes.[14] A high frequency and intensity of PT has shown favorable effects on functional outcomes in CD and possibly on neuroplastic changes. An open controlled study on writer's cramp confirmed that a personalized PT program is able to reorganize maladaptive changes on the sensory-motor cortices in patients, combined with clinical improvements of writing.[31] Unfortunately, confirming these mechanisms in CD is difficult since the cortical representation of neck muscles is rather small. A possible tool to map the cortical representation of the sternocleidomastoid muscle is transcranial magnetic stimulation but research has been limited so far. [32] Future studies towards changes in cortical representation between patients and healthy controls after PT, would expand our knowledge on the pathophysiology of CD and the effects of PT.

## Limitations

This study had some limitations. First there was a large number (n=24) of dropouts, mainly in the RPT group after 12 months. A sensitivity analysis between both groups with imputed and

non-imputed data showed no significant differences in results. A double-blinded trial would be optimal to prevent drop-outs in the control group but this is impossible in PT studies. Secondly, no data was gathered on compliance to the home exercises. Patients in the SPT group may have performed less exercises than prescribed due to limited supervision. Limited supervision makes it hard to obtain reliable data on treatment compliance. Future studies can overcome this by applying health technology like activity trackers. Finally, the effects between the PT programs were smaller than anticipated. In retrospect, an additional effect of 3.5 points on the TWSTRS disability scale may have been over-optimistic. The effect found in this study was 1.71 points, and more in line with the short-term studies with an extra effect of 1.6 and 2.9 points.[9,12] These studies have been published after the start of our study so the power could not be estimated based on these outcomes. However, a change of 3 points on the TWSTRS total score is considered a minimally clinical important change (MCIC).[33] Although there are no references on the MCIC for the separate subscales, a 1.71 point change, which is well over a third of the total MCIC, might be considered as a clinical relevant change for the disability subscale.

## CONCLUSION

We conclude that a specialized PT program revealed no significant differences on disability compared to regular PT after 12 months of treatment.

With similar effects, lower treatment costs, better self-perceived improvement and health perceptions compared to RPT, the SPT program seems to be a suitable alternative for PT treatment of CD.

## ACKNOWLEDGEMENTS

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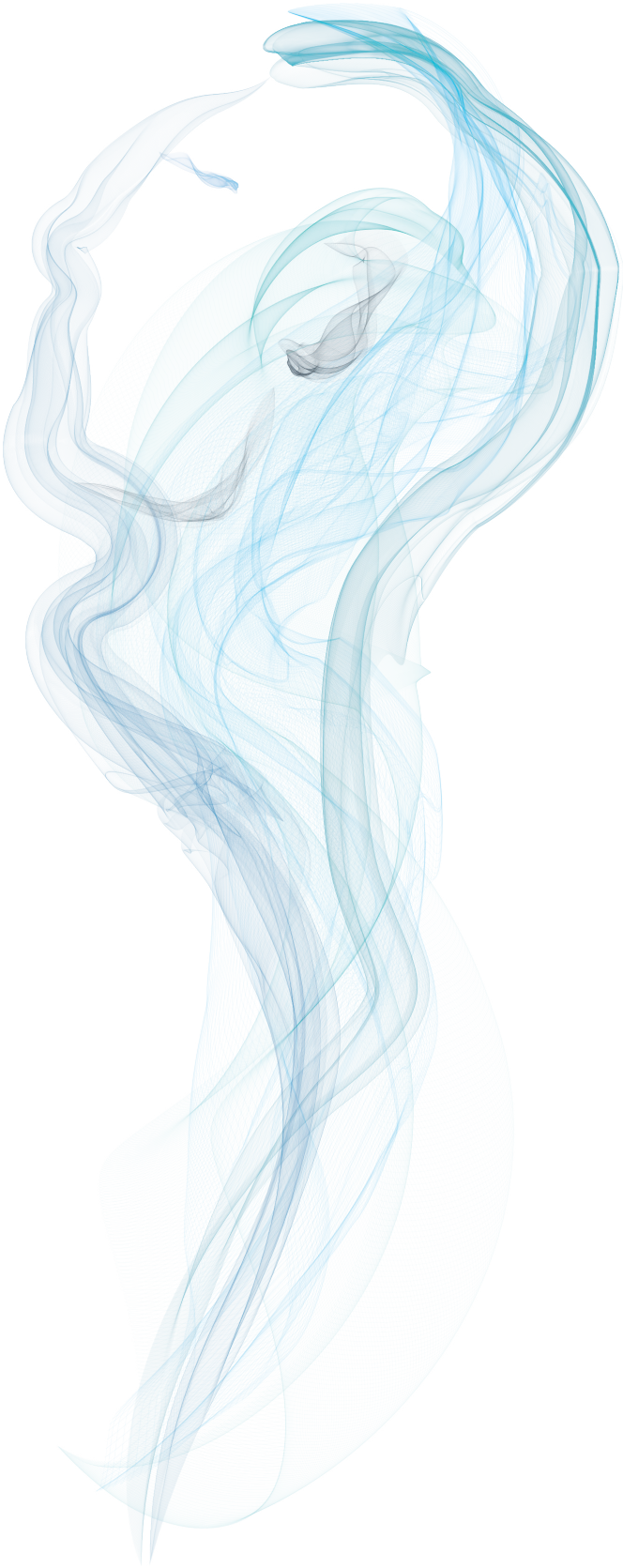


# CHAPTER 6

## Summary and General discussion

Despite remarkable improvements during the last decades, there are still many unmet needs that remain open in the treatment of cervical dystonia (CD) (**Chapter 1**).[1] The aim of this thesis was to explore some of these unmet needs and provide strategies for clinicians to apply in their daily practice.

The first goal was to assess clinical issues in BoNT treatment that need further improvement and to define clinical recommendations for clinicians (**Chapter 2**).

The second goal was to explore which determinants play an important role in disability of CD patients (**Chapter 3a and 3b**) and the third goal was to develop a specialized PT program and to evaluate its effects on disability (**Chapter 4 and 5)**.

This last chapter (**Chapter 6**) includes a summary of the findings of all chapters. Subsequently, the results will be incorporated with existing knowledge in the general discussion. Finally, directions for future research and implementation in healthcare for CD patients will be discussed.

## SUMMARY

In **chapter 2** a systematic review of the literature on botulinum toxin treatment for CD was performed with the aim to provide evidence based practical recommendations for the treating clinicians. Results show a robust body of evidence supporting a good beneficial effect of the different formulations of BoNT in the treatment of CD, with sustained effects over time. However, much debate exists on clinical issues like optimal treatment intervals, dose equivalence between different BoNT formulations, the use of supportive techniques like electromyography or ultrasound and additional therapies like physical therapy. Established strategies to prevent or manage common side effects (including excessive muscle weakness, pain at injection site, dysphagia) and potential contraindications to this treatment (pregnancy and lactation, use of anticoagulants, neurological comorbidities) should also be further explored.

In **Chapter 3a** we explored which factors determine the level of disability in CD patients treated with BoNT on the baseline data from the physical therapy study. A Principal Component Analysis (PCA) revealed four components (psychological features, pain, physical function and severity of dystonia), explaining 74.4% of the variance in disability. Multiple regression analysis showed that psychological features like anxiety and depression contribute significantly to disability (p=.000) followed by pain (p=.004). Interestingly, physical functioning (p=.507) and severity of CD (p=.991) showed no significant contributions to disability. A limitation of this study was that data was collected just prior to the BoNT injections, so the effects of BoNT were minimal. At the peak effect of BoNT, pain might have contributed less to the explanation of disability. It is therefore not clear how generalizable the association of pain is to the overall experience of patients with CD who are

treated with BoNT injections. It is of interest that the motor severity prior to the BoNT injections is also at its worst but is not an important factor on disability. These results highlight the importance of a multidisciplinary approach, including psychological treatment to treat non-motor symptoms in CD in order to improve treatment results.

In **Chapter 3b** we investigated the influence of CD in the performance of an important daily life task; driving a car. Driving performance of 10 patients were compared to 10 healthy controls matched for age and gender. Driving performance was measured with the Standard Deviation of the Lateral Position on the road (SDLP) on a lane tracking ride, gap acceptance time on an intersections ride and deceleration of the rear car during a merging task on a highway. Findings in this explorative pilot study showed no indications that driving performance was significant different from healthy controls on any of the simulated rides (SDLP: p=.853, Gap acceptance time: p=.908, deceleration rear car: p=.169). A limitation of this study was that the simulator rides were relatively short and did not provoke any differences. Furthermore no measures for head or eye movement and gaze direction were incorporated so compensations on this level could not be recorded. Despite these limitations, the results provide an indications that the ability to drive a car is not significantly different in CD patients compared to healthy controls although more comprehensive research with on-road driving tests is needed to confirm this.

**Chapter 4** describes the design and the study protocol of a randomized clinical trial on the effectiveness of an additional standardized PT program to BoNT treatment compared to regular PT in 96 patients with CD. In **chapter 5** the results of the study are presented and show that PT in general is effective to improve disability measured with the TWSTRS disability subscale, but that a specialized PT program is not significant better after 12 months of treatment (between group difference p=.326, within group difference p<.001). Positive results in the standardized PT group were higher patient perceived effects and general health perception. Treatment costs were also lower in the SPT group with an average of 240 US dollars per patient (209 Euro).The effects between the two PT interventions were smaller than anticipated. This could be explained by the possible small contrast between the experimental and control intervention. Standardized PT was largely based on the Bleton method. Control therapists with little knowledge about CD probably searched for suitable treatment methods and also applied the Bleton method. However, with lower costs and similar effects, the SPT program seems to be the preferred program to treat CD.



## GENERAL DISCUSSION

Injections with botulinum neurotoxin in the affected muscles is the preferred treatment for CD. [2–5] There is a robust body of evidence for good beneficial effects of BoNT also in the long-term, yet many issues still remain open in the management of CD as many patients report low levels of treatment satisfaction. Many reasons for low levels of treatment satisfaction exist. Some of

the future challenges that can improve treatment of CD and increase treatment satisfaction are discussed below.

## Determinants of disability

Disability, or the limitations in the ability to perform activities and participation in daily life situations, is an important treatment outcome in the management of CD. In chapter 3 we have demonstrated that disability is mainly determined by psychological factors and pain, rather than the severity of motor symptoms. Improving motor symptoms can help to improve disability by decreasing the feeling of stigma or a negative body concept because the reduction of involuntary movements or postures may also reduce the feeling of being ashamed.[6,7] However, it appears that improving motor symptoms alone is insufficient to substantially decrease disability. A study by Zetterberg et al. towards self-perceived non-motor symptoms in CD showed that self-efficacy is an important contributor to the ability of performing daily life tasks.[8] According to Bandura et al. self-efficacy is not a measure of a skill that an individual possesses, but a belief in what he or she can do under certain conditions and when influenced by difficult circumstances like having a chronic condition.[9] This may explain why some patients with severe motor symptoms report low levels of disability while patients with milder motor symptoms report higher levels of disability. Furthermore, several studies have shown that psychiatric comorbidities like anxiety and depression are significant higher in patients with CD compared to the healthy population but also to patients with other chronic medical conditions.[6,10,11] These findings suggest that psychiatric comorbidities are not only the consequence having a chronic condition but are also a feature of CD itself. [12] Either way, as a consequence or as a feature of CD, psychiatric comorbidities contribute to disability. Therefore, BoNT treatment alone, which is primarily aimed at reducing motor symptoms, is often not sufficient for satisfying treatment results from a patient's point of view.

## The value of PT

Physical therapy is a valuable part of the management of CD. As shown in several smaller studies and chapter 5, PT reduces the level of disability. [13–15] PT contributes to the reduction of disability in several ways.

First, the emphasis of PT is on increasing the ability to perform daily life activities. Besides training to perform the actual daily life task itself, it helps patients to experience their abilities despite physical limitations. This will help to gain confidence and increase self-efficacy, psychological factors which are important contributors to disability. [8,9]

Secondly, pain which is another major contributor to disability, also improves although it is not the primary aim of PT in CD.[13–16] It is thought that pain in CD is mainly related to involuntary muscle contractions, explaining why pain decreases with BoNT treatment.[17–19] However, pain further decreases substantially after PT in addition to BoNT treatment.[13–16] The main thought behind this effect is that by training the antagonist muscles, patients are better able to maintain normal

head postures and perform voluntary movements. Therefore, dystonic activity of the muscles decreases causing less pain.

Another possibility is that PT influences afferent input and alters maladaptive neuroplastic changes which may also decrease pain. Although motor symptoms are the most obvious symptom in focal dystonia's, sensory deficits have been found and it is recognised that the sensory system plays an important role in this condition.[20–23] The sensory aspects of dystonia include abnormalities in temporal or spatial discrimination and the effects of abnormal postural input due to continuous muscle contractrions.[23] So continuous muscle contractions may not only cause pain due to the painful contractions themselves, but the abnormal postural input and chronic nociceptive input from the painful contractions also induces prolonged changes in somatosensory processing and neuronal excitability of the motor cortex.[24] As a consequence, efferent output also changes resulting in loss of motor inhibition and pain. [24,25] By training voluntary movement control and normal head postures, PT could help normalize the abnormal external sensory input and possibly alter the prolonged changes in somatosensory processing. This could cause a further decrease of pain in addition to the effects of BoNT treatment.

A third valuable effect of PT is that there are indications that it prolongs the effect of BoNT. A small trial by Tassorelli et al. comparing the effects of BoNT alone versus BoNT with additional PT showed that the BoNT + PT group had an average prolonged effect of 20 days compared to the group receiving only BoNT injections (99 vs 119 days).[13] One of the advantages of this prolonged effect is that it smoothens the BoNT treatment (figure 3). Normally a peak effect occurs within 2–4 weeks after injections and is followed by a decrease of effect and return of symptoms. On average new injections are given within three months after the previous injections. In chapter 5 we demonstrated improvements on pain and disability after PT, which were measured just prior to the BoNT injections and similar findings were done in a trial towards the effects of PT by Counsell et al.[16]

These findings indicate that PT enhances the beneficial effects of BoNT injections. Therefore new BoNT injections can be given before patients start to experience a serious return of symptoms, improving the overall quality of treatment.

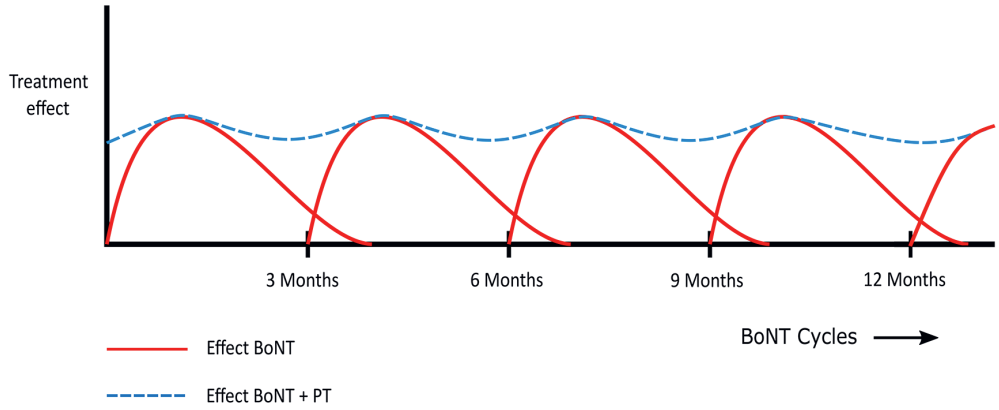


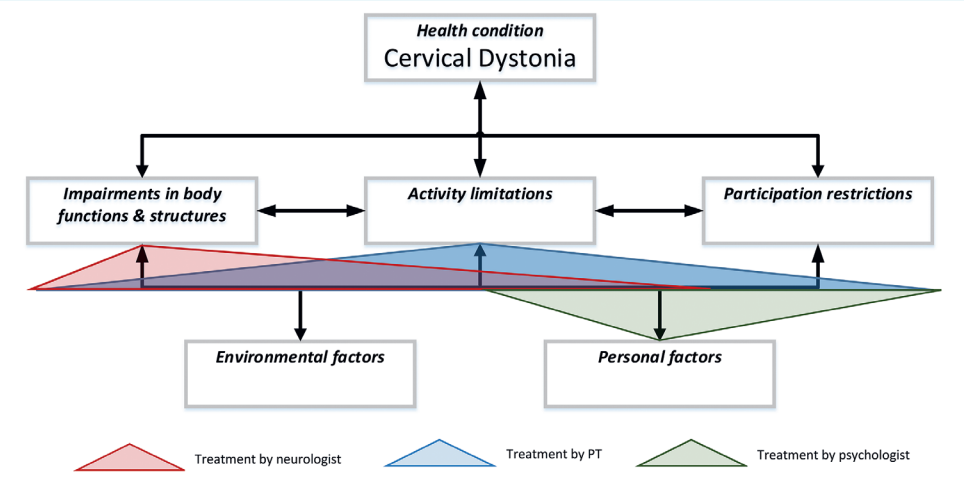

**Figure 3.** Schematic overview of PT effect in addition to BoNT treatment

## Managing cervical dystonia; towards a multidisciplinary approach

As mentioned in the introduction of this thesis, disability is defined by a complex interaction of problems and/or limitations in functions, activities and participation, combined with personal factors and environmental factors according the ICF. [26] Putting the management of CD in perspective of the ICF model, a multi-disciplinary approach should be considered since different healthcare disciplines provide treatment with an emphasis in different domains that define health and disability (Box 1).

BoNT treatment, which is currently the preferred treatment, mainly affects the body functions & structures domain which is just one aspect of the spectrum that defines disability (Box 1). Psychological factors, which are a large contributor to disability in CD patients, mostly affect the personal factors domain while PT mostly affects the activities domain.[6,8,27–29] In order to further improve treatment and decrease levels of disability, multiple domains of the ICF-model should be involved. BoNT treatment should therefore be a part of the overall treatment with additional interventions affecting other aspects of CD. Therefore a multidisciplinary approach, including PT and a more active role for a psychologist or psychiatrist should be considered to improve the overall treatment of CD patients and increase treatment satisfaction.

**Box 1.** Schematic overview of the emphasis of treatment by healthcare providers on the different ICF domains




Explanation:
Treatment by the neurologist is mainly aimed at improving body functions and structures. For example, treatment with BoNT blocks the neuromuscular transmission causing a decrease in dystonic activity of the affected muscle. This also influences the ability to perform activities because patients are therefore able to turn their head in a more controlled and voluntary way.

The emphasis of PT is to perform activities and apply them in daily life situations, for example performing controlled head movements to watch for oncoming traffic before crossing a street. Practicing these activities also affect body functions and structures by gaining strength in the antagonist muscles and more postural control. PT also influences participation restriction. By improving postural control and movements of the head, patients may also become more able to participate in social activities.

Psychological treatment has its emphasis on the personal factors domain. By helping to cope with their anxiety, depression or feeling of stigma, patients gain enough self-confidence and self-efficacy to perform daily life activities and engage in social activities. The domains of activities and participation are therefore also influenced.

Involving more disciplines like PT's and psychologists that affect multiple domains that define health and disability to the needs of the patient can improve the overall treatment and therefore also the treatment satisfaction.

## Future directions for research

It is evident that BoNT treatment is an effective treatment for CD that benefits many patients. However, there is still room for improvement and it is clear that more aspects of CD, besides the motor symptoms, need to be addressed to come to a more effective treatment. Future challenges are to further improve the efficacy of BoNT treatment and to develop a solid body of evidence towards the effects of PT and psychological interventions.

As discussed in chapter 2, clinical issues on optimal treatment intervals, dose equivalence between different BoNT formulations, the use of supportive techniques like electromyography or ultrasound and managing side effects of BoNT therapy remain and need to be further investigated in future studies. These aspects will help improve BoNT treatment and decrease the fluctuation of its effects which still occur in many patients. A more stable effect of BoNT may also improve the combined effects of BoNT and PT treatment. Fluctuations of BoNT effects cause changes in postural feedback and propriocepsis throughout the cycles of BoNT treatment. Coping with these fluctuations are challenging for patients and are likely to interfere with the PT program. The more fluctuations in BoNT effects the more adjustments in the PT program are required. A more stable BoNT treatment and a more constant decrease of the effects until the next BoNT injections will make it easier for patients to adapt to PT and exercises. Investigating techniques that help to further optimize BoNT treatment will therefore not only increase the effectiveness of BoNT but possibly also the effectiveness of PT

Important issues concerning PT that need further investigation are the determination of the right interventions, optimal frequency of treatment and the optimal intensity of treatment. Since many studies towards the effects of PT in CD use a combination of different interventions like training of the antagonist muscles, stretching and relaxation therapy it is difficult to determine which intervention works best (black box).[30,31] However, it is common for PT's to use multiple interventions to achieve a certain treatment goal and not just a single intervention. As described in the specialized PT program (chapter 5) for example, muscle stretching and mobilisations can be used to create sufficient range of motion in the neck before training of the antagonist muscles and daily life tasks can begin. It should therefore be interesting to investigate which 'set' of interventions is the most effective for the treatment of CD and to determine a standardized or core set of interventions. In this way a more uniform treatment can be developed which can aid future studies to investigate the effectiveness of PT treatment.

Besides the types of interventions, treatment effects also depend on the right frequency and intensity of the administered interventions. Based on exercise physiology, motor learning theories, and treatment goals, proper intensity and frequency can be determined as we have attempted in the specialized PT program. However, these theories are based on healthy persons and patients that suffered structural brain damage due to a stroke or accident.[32,33] There is still much uncertainty about the effects in patients with dystonia which is can be considered as a network disorder

without structural brain damage.[34] Having a standardized or core set of PT interventions may help future studies to determine the proper treatment frequency and intensity for patients with CD. By applying the core set of interventions with different frequencies and intensities in a clinical trial, an optimum can be determined for CD patients. Feasibility in relation to the clinical practice must be taken into account when determining this optimum so that the PT treatment can actually be implemented.

The success of PT very much depends on the adherence to treatment and the establishment of behavioural changes to cope with their chronic condition in a healthy way. To reach treatment goals and enable patients to successful manage their condition, patients need to learn how to train independently. However, it is challenging to monitor treatment adherence in a reliable way. A solution may be found in E-health with sensor technology. Sensors that send real-time training information to healthcare providers could help them to monitor treatment progression and adherence.

To motivate patients and to promote changes that benefit healthy behaviour, persuasive technologies may be useful in the management of CD. Persuasive technology are interactive systems designed to aid and motivate people to adopt behaviours that are beneficial to them and their community while avoiding harmful ones.[35] A simple example of such an intervention is a reminder system that alerts users when it is time to engage in a healthy behaviour, such as exercising or taking medication on a smartphone. Future studies should focus on the development and implementation of these kind of technologies in the management of CD. Subsequently it should be investigated whether E-health and persuasive technologies contribute to the efficacy of PT treatment.



Combining these studies with techniques like functional magnetic resonance (fMRI) or transcranial magnetic stimulation (TMS) with paired associative stimulation protocols (PAS), would enable to show changes in brain area's that are known to be affected in CD and if these changes are altered or normalized with PT treatment. If these changes are also accompanied with clinical improvement after PT, the effectiveness of PT treatment can be demonstrated.

## Future directions in healthcare for CD patients

Since recent years it has become more evident that a multidisciplinary treatment approach is more beneficial for CD patients than treatment which is aimed at reducing motor symptoms alone. As we have demonstrated in our PT trial (chapter 5), PT is a useful addition to BoNT treatment. In our study towards determinants of disability (chapter 4) we have shown that psychological factors are very important contributors to disability and that it is recommended to include psychological treatment in the overall treatment of CD for the patients who need it.

However, when PT's and psychologists are incorporated in the treatment of CD, it is necessary to have a good communication infrastructure between the different disciplines in order to coordinate the treatment. This could be organized in local networks with caregivers who have a special interest in CD and are sufficiently trained. A good example of such a network is the Dutch ParkinsonNet.[36] Specialised physiotherapy delivered through trained ParkinsonNet PT's is associated with fewer Parkinson's disease-related complications and lower treatment costs.[36] At ParkinsonNet, it is a neurologist who facilitate specialised physiotherapy by specific referral to trained therapists.

Following this example the DystoniaNet was founded in 2010 with the aim of more cooperation on education, research and treatment between neurologists and allied healthcare professionals with a special interest in CD. Currently training is given to neurologists and specialized nurses to improve their skills concerning BoNT treatment. Based on the results and experiences from our PT study it is planned to organize training for PT's so neurologists can refer patients to these experts. In the future more disciplines like psychologists will be involved in the DystoniaNet to create a network with specialized caregivers for CD.

## CONCLUSIONS

This thesis showed that despite the abundant evidence towards the effectiveness of BoNT treatment in CD, there is still room for improvement. Further research is needed towards optimal treatment intervals, dose equivalence between different BoNT formulations, the use of supportive techniques like electromyography or ultrasound and managing side effects of BoNT therapy. Secondly, we found that PT is a valuable addition to BoNT treatment to improve disability and pain. Finally, we found that psychological factors are important determinants of disability. Based on these findings and the definition of health as defined by the ICF, a multidisciplinary treatment approach to further improve the treatment and quality of life for CD patients is recommended.

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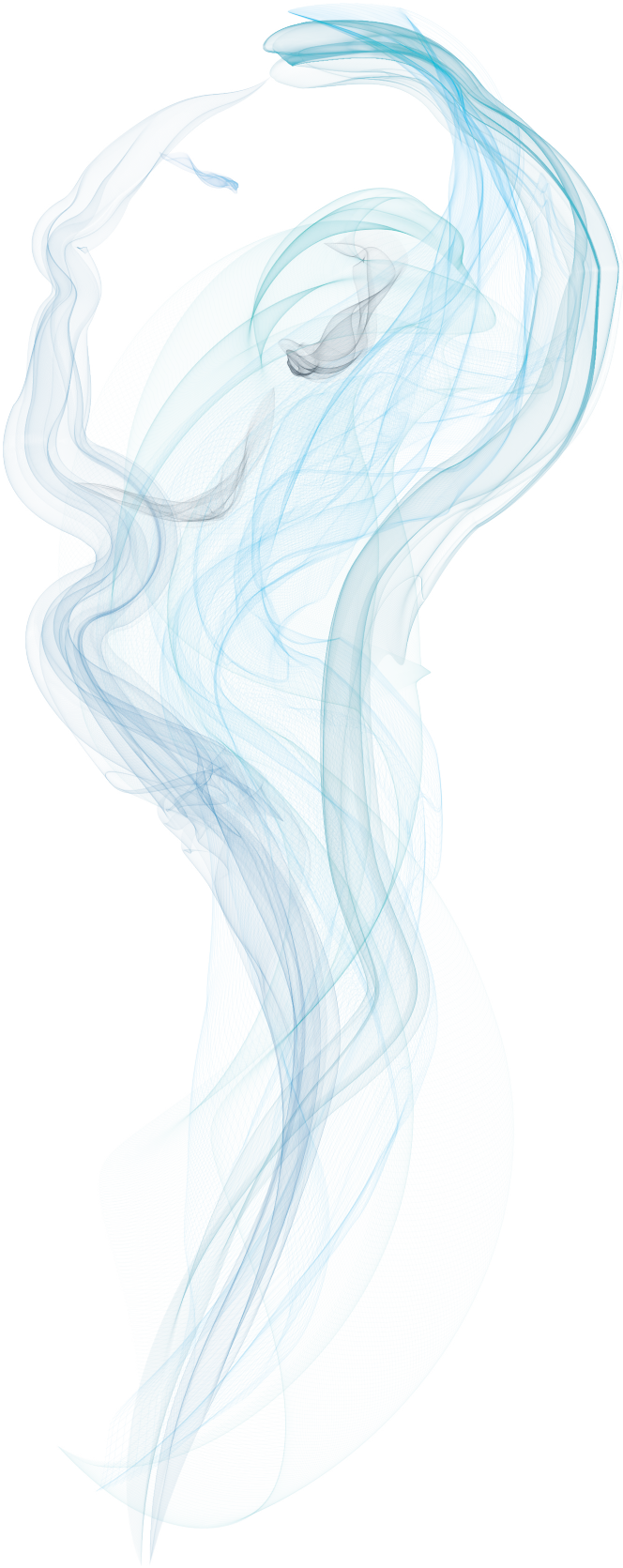

# APPENDICES

# DUTCH SUMMARY / NEDERLANDSE SAMENVATTING

Dit proefschrift gaat over de behandeling van cervicale dystonie (CD), welke determinanten een belangrijke rol spelen bij de beperkingen die patiënten in het dagelijks leven ervaren en de toegevoegde waarde van fysio-/oefentherapie bij het verminderen van deze beperkingen.

Dystonie is een invaliderende, neurologische bewegingsstoornis die wordt gekenmerkt door onvrijwillige en wisselende samentrekkingen van spieren, waardoor er abnormale, vaak repetitieve bewegingen en/of houdingen ontstaan. Bij cervicale dystonie komen deze abnormale en onvrijwillige bewegingen vooral voor in de nek resulterend in abnormale houdingen en schuddende of wringende bewegingen van het hoofd. Een ander veelvoorkomend aspect van CD is de *geste antagonistique* oftewel de *sensory trick*. Hierbij kunnen de motorische symptomen tijdelijk worden onderdrukt door zachte aanraking van de wang of de achterzijde van het hoofd.

Symptomen starten over het algemeen na de leeftijd van 30 jaar met een piek tussen het 50$^{ste}$ en 60$^{ste}$ levensjaar.

Naast de motorische symptomen ondervinden veel patiënten ook niet-motorische symptomen. Ongeveer 75% van de patiënten ervaart pijn. Andere niet-motorische symptomen zijn angst, depressie en slaapstoornissen. De prevalentie van psychische klachten kan oplopen tot ruim 91% vergeleken met 35% in de algehele populatie. Dit kan het gevolg zijn van leven met een chronische, zichtbare en invaliderende aandoening. Echter, vergeleken met patiënten met andere chronische aandoeningen hebben patiënten met cervicale dystonie nog steeds een significant hoger risico op psychische klachten. Niet-motorische symptomen worden tevens geassocieerd met een verminderde kwaliteit van leven en een verminderd vermogen om dagelijkse activiteiten uit te voeren.

De oorzaak van CD, en dystonie in het algemeen, is nog grotendeels onbekend. De algemene gedachte is dat dystonie wordt veroorzaakt door een genetische predispositie in combinatie met externe factoren, zoals een trauma, stress of het maken van veel repetitieve bewegingen, waardoor er veranderingen op meerdere niveaus van het centrale zenuwstelsel ontstaan die leiden tot de onwillekeurige bewegingen.

De eerstekeusbehandeling van CD is injecties met botulinetoxine (BoNT) in de aangedane spieren. BoNT blokkeert de neuromusculaire signaaloverdracht, waardoor de spiercontracties verminderen en de aangedane spier ontspant. Hoewel BoNT-injecties een bewezen effectieve methode zijn om de motorische symptomen te verminderen, blijven patiënten vaak problemen houden met het uitvoeren van dagelijkse taken. De effectiviteit van de BoNT-behandeling is afhankelijk van vele factoren zoals de juiste dosering, de juiste selectie van aangedane spieren, de juiste plaats van injecteren en de ervaring van de zorgverlener die de injecties toedient.

Naast de behandeling met BoNT-injecties worden patiënten vaak doorverwezen voor fysio-/oefentherapie om hun problemen met het uitvoeren van dagelijkse activiteiten te verbeteren. Voor de effectiviteit van de fysio-/oefentherapeutische behandeling is slechts beperkt bewijs. Daarnaast hebben veel therapeuten weinig ervaring met de behandeling van CD, omdat ze maar weinig patiënten zien door de relatieve zeldzaamheid van de aandoening.

Om de behandeling van CD te verbeteren, heeft dit proefschrift om te beginnen als doel klinische kwesties in de botulinebehandeling te onderzoeken die verdere verbetering behoeven, en om hiervoor aanbevelingen en behandelstrategieën te formulieren die zorgverleners bij de behandeling in de dagelijkse praktijk kunnen gebruiken om deze te verbeteren (**Hoofdstuk 2**).

Het tweede doel is om te onderzoeken welke determinanten een belangrijke rol spelen bij de beperkingen die patiënten in het dagelijks leven ervaren (**Hoofdstuk 3a en 3b**).

Het derde en laatste doel is om een gestandaardiseerd behandelprogramma voor fysio- en oefentherapeuten te ontwikkelen en om de effectiviteit hiervan te testen op het verminderen van de beperkingen in het dagelijks leven (**Hoofdstuk 4 en 5**).

## SAMENVATTING

**Hoofdstuk 2** is een systematische review van de literatuur over de BoNT-behandeling van CD. Het doel van deze review was om tot praktische evidence based aanbevelingen te komen die behandelende zorgverleners kunnen gebruiken in de dagelijkse praktijk. De resultaten lieten een hoge mate van bewijs zien voor de positieve effecten van de verschillende BoNT formules met een langdurig effect over de tijd. Er bestaat echter veel discussie over klinische kwesties zoals de optimale behandelinterval, de juiste verhouding tussen de dosering van verschillende BoNT-formules, het gebruik van ondersteunende technieken om de juiste spieren te selecteren zoals EMG- of echobegeleiding en additionele therapieën zoals fysio-/oefentherapie. Verder lieten de resultaten zien dat bestaande strategieën om veelvoorkomende bijwerkingen (spierzwakte, dysfagie, pijn) en mogelijke contra-indicaties (zwangerschap, lactatie, gebruik van bloedverdunners en neurologische comorbiditeiten) te voorkomen of te behandelen nader onderzocht dienen te worden.

In **hoofdstuk 3a** zijn de factoren onderzocht, die bepalen in welke mate patiënten met CD beperkt zijn in het uitvoeren van dagelijkse activiteiten met baselinedata uit de studie naar de effectiviteit van fysio-/oefentherapie bij CD. Een principale componentenanalyse (PCA) liet vier componenten zien (psychologische aspecten, pijn, fysiek functioneren en de ernst van de dystonie) die 74.4% verklaarden van de variantie van disability. Een multiple regressieanalyse liet zien dat psychologische aspecten, zoals angst en depressie (p=.000), evenals pijn (p=.004),

significant (p=.000) bijdragen aan disability. Opmerkelijk genoeg leveren fysiek functioneren (p=.507) en de ernst van de dystonie (p=.991) geen significante bijdrage.

Een beperking van deze studie is dat de data vlak voor de BoNT-injecties is verzameld, waardoor de effecten van de BoNT minimaal waren. Als de data was verzameld op het moment dat de BoNT het effectiefst was, zou pijn wellicht minder hebben bijgedragen aan de variantie van disability. Het is daardoor nog niet geheel duidelijk hoe generaliseerbaar de associatie van pijn met disability is in CD.

Opmerkelijk is dat de ernst van de dystonie geen associatie heeft met disability. Ook niet op het moment dat de effecten van BoNT minimaal zijn. De resultaten van deze studie onderschrijven het belang van een multidisciplinaire aanpak, inclusief de psychologische hulp indien nodig, om de behandeling van CD te verbeteren.

In **hoofdstuk 3b** is de invloed van CD op de rijvaardigheid, een belangrijke dagelijkse activiteit, geëvalueerd in een rijsimulator. De rijvaardigheid van 10 patiënten is vergeleken met 10 gezonde controlepersonen die zijn gekoppeld op leeftijd en geslacht. Rijvaardigheid is gemeten met de Standaarddeviatie van de laterale positie (SDLP) op de weg tijdens een slingerrit, gap acceptance tijd op een kruispuntenroute en de vertraging van een achterop naderende auto tijdens een invoegtaak op de snelweg. Bevindingen van deze verkennende pilotstudie lieten geen indicaties zien dat de rijvaardigheid van CD-patiënten significant verschilt van gezonde controlepersonen (SDLP: p=.853, gap acceptance tijd: p=.908, vertraging van achterop naderende auto: p=.169). Een beperking van deze studie was dat de ritten relatief kort waren. Hierdoor is mogelijk geen verschil tussen de groepen zichtbaar geworden. In de praktijk zijn er patiënten die aangeven dat ze alleen korte stukken of niet te lang achter elkaar rijden, omdat anders een verergering van de dystone activiteit optreet. Langere ritten zouden de beperkingen wellicht beter zichtbaar maken. Daarnaast zijn er geen uitkomstmaten voor oog- en hoofdbewegingen meegenomen om mogelijke mechanismen in kaart te brengen die compenseren voor het verminderde vermogen van patiënten om gecontroleerde bewegingen te maken. Uitgebreider onderzoek met langere ritten is nodig om de bevindingen van deze pilotstudie te bevestigen.

**Hoofdstuk 4** beschrijft het ontwerp en protocol van een gerandomiseerd onderzoek naar de effectiviteit van een gestandaardiseerd fysio-/oefentherapieprogramma in combinatie met de BoNT-behandeling. Het gestandaardiseerde behandelprogramma wordt hierbij vergeleken met reguliere fysio-/oefentherapie bij 96 patiënten met CD. In **hoofdstuk 5** worden de resultaten van deze studie gepresenteerd. Deze studie liet zien dat fysio-/oefentherapie in algemene zin een positief effect heeft op het verminderen van disability, zoals gemeten met de TWSTRS disability subschaal. Beide groepen lieten een significante verbetering zien na een jaar therapie (p<.001), maar de groepen verschilden niet significant van elkaar (p=.326). Wel lieten de patiënten uit de groep met gestandaardiseerde therapie grotere zelf gerapporteerde vooruitgang zien en een

betere gezondheidsperceptie, gemeten met de SF-36 kwaliteit van leven schaal. Daarnaast waren de behandelkosten gemiddeld 209 euro lager in de groep die gestandaardiseerde fysio-/oefentherapie kreeg.

Een beperking van deze studie was dat het verschil tussen beide groepen kleiner was dan verwacht. Gestandaardiseerde fysio-/oefentherapie is deels gebaseerd op de Bleton-methode. Therapeuten uit de controlegroep, met minder kennis op het gebied van CD hebben waarschijnlijk gezocht naar beschikbare behandelmethoden waarbij ze gebruik hebben gemaakt van de Bleton-methode. Echter, met lagere kosten en vergelijkbare effecten op disability heeft het de voorkeur om CD-patiënten met het gestandaardiseerde behandelprogramma te behandelen.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADL | Activities of Daily Living |
| BAI | Beck Anxiety Index |
| BDI | Beck Depression Index |
| BoNT | Botulinum Toxin |
| BTX | Botulinum Toxin |
| CD | Cervical Dystonia |
| CDQ-24 | Craniocervical Dystonia Questionnaire |
| CMAP | Compound Muscle Action Potential |
| DBS | Deep brain Stimulation |
| EMG | Electromyography |
| FDQ | Functional Disability Questionnaire |
| FTDS | Fitness To Drive Screening |
| ICF | International Classification of Functioning |
| NAB | Neutralizing Anti Bodies |
| NRS | Numeric Rating Scale |
| PCA | Principal Component Analysis |
| PCQ | Productivity Cost Questionnaire |
| PT | Physical Therapy |
| QoL | Quality of Life |
| RCT | Randomized Controlled Trial |
| RPT | Regular Physical Therapy |
| SDLP | Standard Deviation of the Lateral Position |
| SF-36 | Short Form 36 |
| SPT | Specialized Physical Therapy |
| SNR | Secundary Non-Responsiveness |
| TWSTRS | Toronto Western Spasmodic Torticollis Rating Scale |

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De aanhouder wint, en dat geldt ook voor het afronden van dit proefschrift. Het van de grond af aan bedenken, opzetten en uitvoeren van een klinische trial is een tijdrovende en bij vlagen frustrerende ervaring geweest. Een klus van bijna 10 jaar die ik voor geen goud had willen missen. Ten eerste, omdat het een bijzonder leerzame ervaring is geweest en ten tweede, omdat ik met een hoop fantastische mensen heb mogen samenwerken, die hebben bijgedragen aan het tot stand komen van mijn proefschrift. Graag wil ik een aantal van deze mensen bedanken voor hun hulp en inzet.

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# CURRICULUM VITAE

Joost van den Dool was born on the first of January 1983 in Alphen aan den Rijn, the Netherlands. In 2001 he completed secondary school (HAVO) at the Coenecoop College in Waddinxveen. He continued to study Physiotherapy at the University of Applied Sciences in Leiden (Hogeschool Leiden). For his bachelor thesis he evaluated the effects of a community based rehabilitation program for children with cerebral palsy in the Kagithane Rehabilitation Unit, Istanbul, Turkey after which he gained his Bachelor of Science degree in 2005. Thereafter he worked as a physiotherapist in several private practices in the Netherlands and Curaçao until 2009. That year he started as research assistant at the neurology department of the Leiden University Medical Center. Under supervision of prof. J.J. van Hilten and dr. D.E. van Rooijen he assisted with several studies on the Complex Regional Pain Syndrome and dystonia within the TREND consortium until 2010. Simultaneously he finished the Pre-master and Master program Clinical Health Sciences at the University of Utrecht in 2011 with his Master thesis *The influences of mirror visual feedback on motor function and pain in upper limb dystonia, related to the Complex Regional Pain Syndrome: a pilot study.*

In 2010 Joost started working at the neurology department of the Academic Medical Center (AMC), University of Amsterdam on the development of a standardized physical therapy program for cervical dystonia under supervision of prof. dr. M.A.J. de Koning-Tijssen. This resulted in a PhD project on the effectiveness of standardized physical therapy on disability in cervical dystonia, that started in 2012 and was co-supervised by dr. B. Visser of the ACHIEVE Centre of Applied Research, Faculty of Health, Amsterdam University of Applied Sciences and dr. J.H.T.M Koelman of the neurology department of the AMC.

Since 2017 Joost is working as a senior researcher at NIVEL, the Netherlands Institute for Health Services Research, where he focuses on research towards allied healthcare in the primary healthcare setting.